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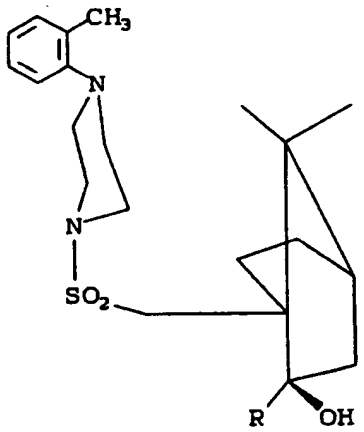
(54) **Substituted derivatives of piperazinylcamphorsulfonyl oxytocin antagonists.**

(57) Compounds of the formula:



wherein R is oxime, hydroxy, halogen, cyclic epoxide, alkylcarbonyloxy, alkoxycarbonylalkoxy, trihaloalkylsulfonyloxo, or unsubstituted or substituted oxo, where said substituent is unsubstituted or substituted saturated 6-membered heterocyclic rings having 1 or 2 heteroatoms which are N, and said substituent is alkyl.

The compounds of formula I are oxytocin antagonists useful in the treatment of preterm labor, dysmenorrhea and for the stoppage of labor preparatory to cesarean delivery. Also disclosed are pharmaceutical compositions containing these compounds, methods of their use and methods of their preparation.

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FIELD OF THE INVENTION

The present invention provides novel compounds, novel compositions, methods of their use and methods of their manufacture, such compounds generally pharmacologically useful as agents in obstetric and gynecologic therapy. The aforementioned pharmacologic activities are useful in the treatment of mammals. More specifically, the compounds of the present invention can be used in the treatment of preterm labor, stopping labor preparatory to Cesarean delivery, and in the treatment of dysmenorrhea. At the present time, there is a need in the area of obstetric and gynecologic therapy for such agents.

BACKGROUND OF THE INVENTION

In the field of obstetrics, one of the most important problems is the management of preterm labor. A significant number of the pregnancies progressing past 20 weeks of gestation experience premature labor and delivery, which is a leading cause of neonatal morbidity and mortality. Despite major advances in neonatal care, retention of the fetus in utero is preferred in most instances.

Tocolytic (uterine-relaxing) agents that are currently in use include β_2-adrenergic agonists, magnesium sulfate and ethanol. Ritodrine, the leading β_2-adrenergic agonist, causes a number of cardiovascular and metabolic side effects in the mother, including tachycardia, increased renin secretion, hyperglycemia (and reactive hypoglycemia in the infant). Other β_2-adrenergic agonists, including terbutaline and albuterol have side effects similar to those of ritodrine. Magnesium sulfate at plasma concentrations above the therapeutic range of 4 to 8 mg/dL can cause inhibition of cardiac conduction and neuromuscular transmission, respiratory depression and cardiac arrest, thus making this agent unsuitable when renal function is impaired. Ethanol is as effective as ritodrine in preventing premature labor, but it does not produce a corresponding reduction in the incidence of fetal respiratory distress that administration of ritodrine does.

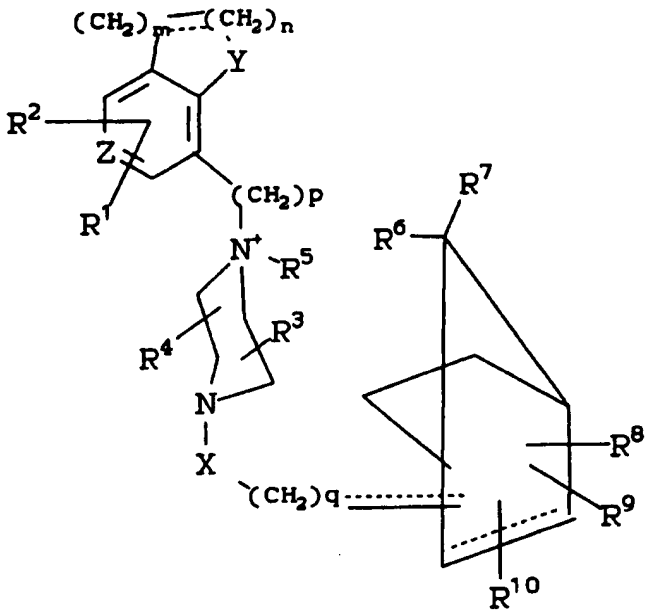
It has been proposed that a selective oxytocin antagonist would be the ideal tocolytic agent. In the last few years, evidence has accumulated to strongly suggest that the hormone oxytocin is the physiological initiator of labor in several mammalian species including humans. Oxytocin is believed to exert this effect in part by directly contracting the uterine myometrium and in part by enhancing the synthesis and release of contractile prostaglandins from the uterine endometrium/decidua. These prostaglandins may, in addition, be important in the cervical ripening process. By these mechanisms, the process of labor (term and preterm) is initiated by a heightened sensitivity of the uterus to oxytocin, resulting in part as a result of a well-documented increase in the number of oxytocin receptors in this tissue. This "up-regulation" of oxytocin receptors and enhanced uterine sensitivity appears to be due to trophic effects of rising plasma levels of estrogen towards term. By blocking oxytocin, one would block both the direct (contractile) and indirect (enhanced prostaglandin synthesis) effects of oxytocin on the uterus. A selective oxytocin blocker, or antagonist, would likely be more efficacious for treating preterm labor than current regimens. In addition, since oxytocin at term has major effects only on the uterus, such an oxytocin antagonizing compound would be expected to have few, if any, side effects.

The compounds of the present invention can also be useful in the treatment of dysmenorrhea. This condition is characterized by cyclic pain associated with menses during ovulatory cycles. The pain is thought to result from uterine contractions and ischemia, probably mediated by the effect of prostaglandins produced in the secretory endometrium. By blocking both the direct and indirect effects of oxytocin on the uterus, a selective oxytocin antagonist can be more efficacious for treating dysmenorrhea then current regimens.

It is, therefore, a purpose of this invention to provide substances which more effectively antagonize the function of oxytocin in disease states in animals, preferably mammals, especially in humans. It is another purpose of this invention to prepare novel compounds which more selectively inhibit oxytocin. It is still another purpose of this invention to provide a method of antagonizing the functions of oxytocin in disease states in mammals. It is also a purpose of this invention to develop a method of preventing or treating oxytocin-related disorders of preterm labor and dysmenorrhea by antagonizing oxytocin.

It has now been found that compounds of formula I are antagonists of oxytocin and bind to the oxytocin receptor. When the oxytocin receptor is bound by the compounds of the present invention, oxytocin is antagonized by being blocked from its receptor and thus being unable to exert its biologic or pharmacologic effects. These compounds are useful in the treatment and prevention of oxytocin-related disorders of animals, preferably mammals and especially humans. Th s disorders are primarily pret rm labor and dysmenorrhea. The compounds would also find usefulness for stoppage of labor preparation to Cesarean delivery.

The compounds f the pr sent invention ar those of the general structural formula:



and the pharmaceutically acceptable salts thereof,

X is
- (1) carbonyl or
- (2) sulfonyl;

Y is
- (1) hydrogen,
- (2) alkyl or
- (3) NH;

Z is
- (1) C or
- (2) N;

R^1 and R^2 are independently
- (1) hydrogen,
- (2) halogen,
- (3) alkoxy,
- (4) alkylsulfonyl or
- (5) unsubstituted or substituted alkyl wherein said substituent is
  - amino,
  - alkyl, or
  - dialkylamino;

R^3 and R^4 are independently
- (1) hydrogen,
- (2) alkyl,
- (3) substituted alkyl when said substituent is
  - amino
  - alkylsulfonyl,
  - arylsulfonyl,
  - alkylamino, or
  - dialkylamino;
- (4) phenylalkyl or
- (5) oxo;

R^5 is
- (1) hydrogen or
- (2) oxo

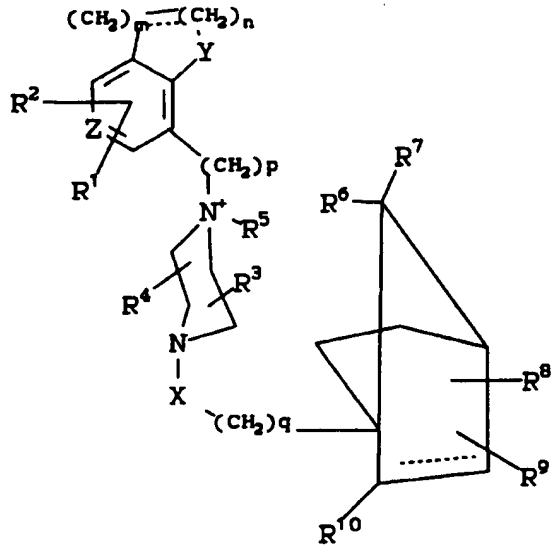
R^6 and R^7 are indep nd ntly

(1) hydrog n,
(2) alkyl or
(3) joined to form unsubstituted or substituted cycloalkyl where said substituent is hydroxy or
hydroxyalkyl;

R^8, R^9 and R^{10} are independently
(1) hydrogen,
(2) oxime,
(3) hydroxy,
(4) halogen,
(5) cyclic epoxide,
(6) alkylcarbonyloxy,
(7) alkoxycarbonylalkoxy,
(8) trihaloalkylsulfonyloxo,
(9) unsubstituted or substituted 5 or 6-membered heterocyclic rings containing 1,2 or 3 heteroatoms where said heteroatom is N,S or O and said substituents are one or more of
oxo or,
C_{1-6} alkyl, optionally substituted by
alkylthio
alkylsulfinyl
alkylsulfonyl
cyano
carboxy,
hydroxy
amine,
alkylamine
dialkylamine
alkoxy
aminocarbonyl,
tetrazolyl
imidazole and
spiro-piperidinyl where the piperidine N is unsubstituted or substituted by C_{1-6} alkyl;
(10) unsubstituted, mono- or di-substituted phenyl where said substituents are independently one or more of
halogen,
carboxy,
alkoxycarbonyl,
carboxyalkyl,
amino,
alkylamino,
dialkylamino,
cyano,
alkylsulfonylamino,
aminoalkyl,
alkylaminoalkyl,
dialkylaminoalkyl; and

m, n, p and q are integers of from 0 to 2.

More particularly preferred compounds are those of the general structural Formula



and the pharmaceutically acceptable salts thereof.

X is
- (1) carbonyl or
- (2) sulfonyl;

Y is
- (1) hydrogen,
- (2) alkyl or
- (3) NH;

Z is
- (1) C or
- (2) N;

R^1 and R^2 are independently
- (1) hydrogen,
- (2) halogen,
- (3) alkoxy,
- (4) alkylsulfonyl or
- (5) unsubstituted or substituted alkyl wherein said substituent is
  - amino,
  - alkylamino or
  - dialkylamino;

R^3 and R^4 are independently
- (1) hydrogen,
- (2) alkyl,
- (3) substituted alkyl where said substituent is
  - amino
  - alkylsolfonyl,
  - arylsulfonyl,
  - alkylamino, or
  - dialkylamino;
- (4) phenyalkyl or
- (5) oxo;

R^5 is
- (1) hydrogen or
- (2) oxo;

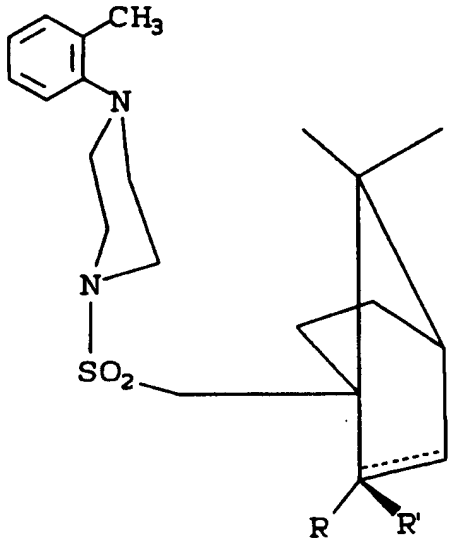
R^6 and R^7 are independently
- (1) hydrogen,
- (2) alkyl or

(3) joined to form unsubstitued or substitut d cycloalkyl where said substituent is
hydroxy or
hydroxyalkyl;

R^8, R^9 and R^{10} are independently
(1) hydrogen,
(2) oxime,
(3) hydroxy,
(4) halogen,
(5) oxo,
(6) cyclic epoxide,
(7) alkylcarbonyloxy,
(8) alkoxycarbonylalkoxy,
(9) trihaloalkylsulfonyloxo,
(10) unsubstituted or substituted 5-membered heterocyclic rings containing 1 or 2 heteroatoms where said heteroatom is N or O and said substituents are
oxo or
C_{1-6} alkyl, optionally substituted by
carboxy,
amine,
aminocarbonyl or
imidazole; and

m, n, p and q are integers from 0 to 2.

Most preferred are those compounds of the general formula



and the pharmaceutically acceptable salts thereof, wherein
R' is an optional substituent that, when present, is H or OH;
R is
(1) hydrogen,
(2) oxime,
(3) hydroxy,
(4) halogen,
(5) cyclic epoxide,
(6) alkylcarbonyloxy,
(7) alkoxycarbonylalkoxy,
(8) trihaloalkylsulfonyloxo,
(9) unsubstituted or substituted 5-membered heterocyclic rings containing 1 or 2 heteroatoms where said heteroatom is N or O and said substitu nts are

oxo or
C_{1-6} alkyl, optionally substituted by
carboxy,
amine,
aminocarbonyl or
imidazole.

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following salts:

Acetate	Lactobionate
Benzenesulfonate	Laurate
Benzoate	Malate
Bicarbonate	Maleate
Bisulfate	Mandelate
Bitartrate	Mesylate
Borate	Methylbromide
Bromide	Methylnitrate
Calcium Edetate	Methylsulfate
Camsylate	Mucate
Carbonate	Napsylate
Chloride	Nitrate
Clavulanate	N-methylglucamine ammonium salt
Citrate	
Dihydrochloride	Oleate
Edetate	Oxalate
Edisylate	Pamoate (Embonate)
Estolate	Palmitate
Esylate	Pantothenate
Fumarate	Phosphate/diphosphate
Gluceptate	Polygalacturonate
Gluconate	Salicylate
Glutamate	Stearate
Glycollylarsanilate	Subacetate
Hexylresorcinate	Succinate
Hydrabamine	Tannate
Hydrobromide	Tartrate
Hydrocloride	Teoclate
Hydroxynaphthoate	Tosylate
Iodide	Triethiodide
Isethionate	Valerate
Lactate	

The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

The term "alkyl" shall mean straight or branched chain alkanes, alkenes and alkynes with one or more degrees of unsaturation at any position on the chain, of one to ten total carbon atoms, or any number within this range.

The term "aryl" shall mean phenyl, naphthyl and fluorenyl.

The term "cycloalkyl" shall mean cyclic rings of alkanes, alkenes or alkynes with one or more degrees of unsaturation at any position of the ring, of three to eight total carbon atoms.

Whenever the terms "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g. aralkoxyaryloxy) they shall be interpreted as including those limitations given above for "alkyl" and "aryl". Designated numbers of carbon atoms (e.g. C_{1-10}) shall refer independently to the number of carbon atoms in an alkyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears

as its prefix root.

Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally.

The term "oxo" shall refer to the substituent =O.

The term "halogen" shall include iodine, bromine, chlorine and fluorine.

The term "preterm labor" shall mean expulsion from the uterus of a viable infant before the normal end of gestation, or more particularly, onset of labor with effacement and dilation of the cervix before the 37th week of gestation. It may or may not be associated with vaginal bleeding or rupture of the membranes.

The term "dysmenorrhea" shall mean painful menstruation.

The term "cesarean delivery" shall mean incision through the abdominal and uterine walls for delivery of a fetus.

The term "substituted" shall be deemed to include multiple degrees of substitution by a named substitutent.

The ability of the compounds of formula I to antagonize oxytocin makes these compounds useful as pharmacologic agents for mammals, especially for humans, for the treatment and prevention of disorders wherein oxytocin may be involved. Examples of such disorders include preterm labor and especially dysmenorrhea. These compounds may also find usefulness for stoppage of labor preparatory to Cesarean delivery.

Because of the known relationship of vasopressin to oxytocin, the compounds of the present invention are also useful as vasopressin antagonists. Vasopressin antagonists are useful in the treatment or prevention of disease states involving vasopressin disorders, including their use as diuretics and their use in congestive heart failure.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as a tocolytic agent.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.3-6.0 gm/day orally. Intravenously, the most preferred doses will range from 0.1 to about 10 mg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylen glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, zanthan gum and the like.

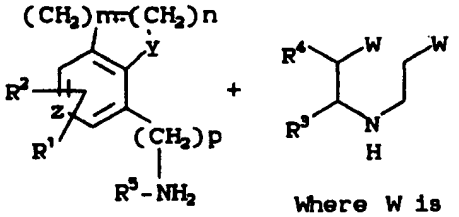
The compounds of th present inv ntion can also be administ red in the form of liposome delivery syst ms, such as small unilamellar v sicles, large unilam llar vesicl s and multilamellar v sicl s. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

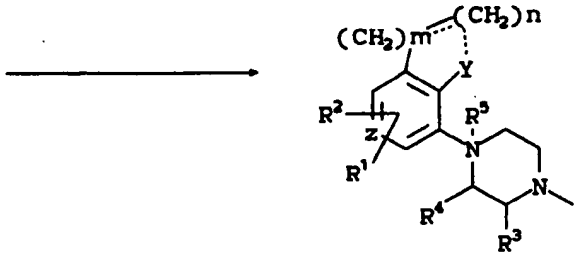
The compounds of formula I can be prepared readily according to the following reaction Schemes (in which all variables are as defined before) and Examples or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

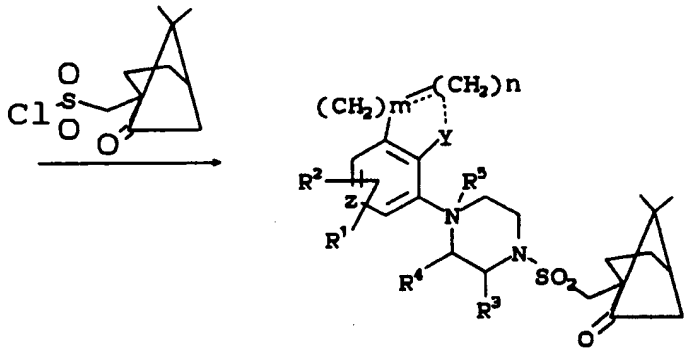
The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless noted otherwise.

SCHEME 1



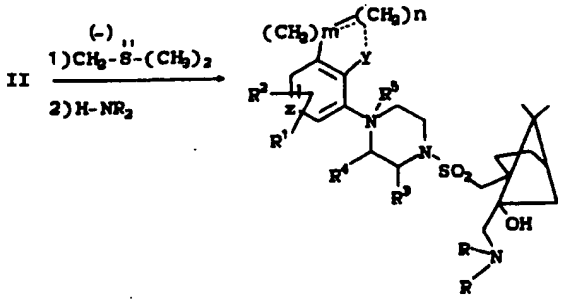
Where W is a suitable leaving group



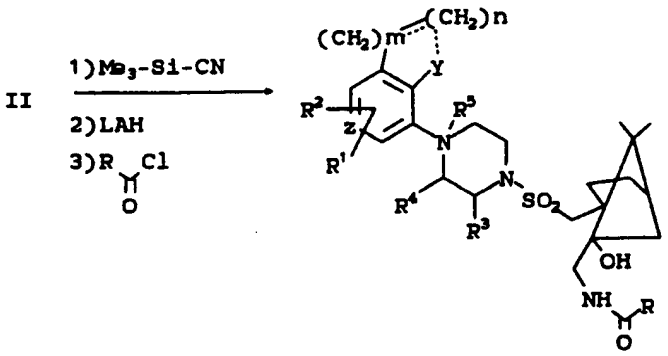


II

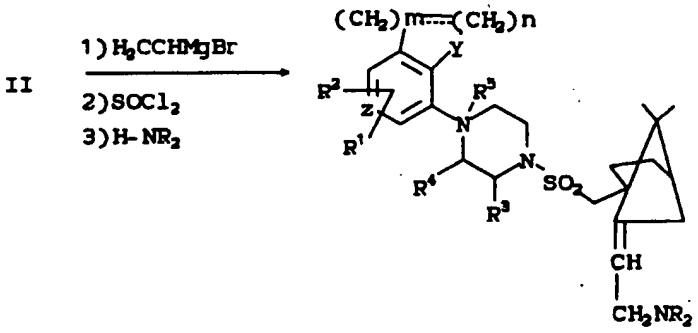
SCHEME 2



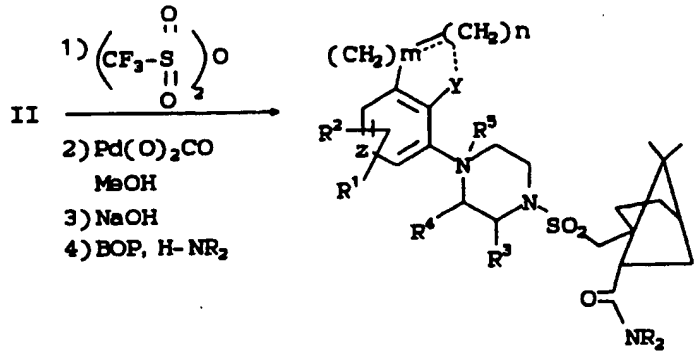
SCHEME 3



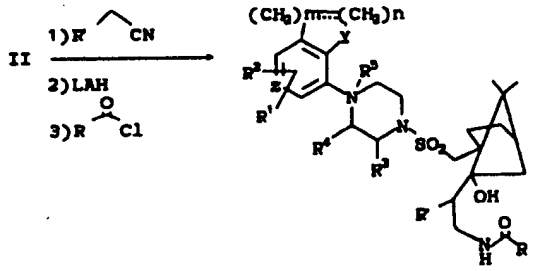
SCHEME 4



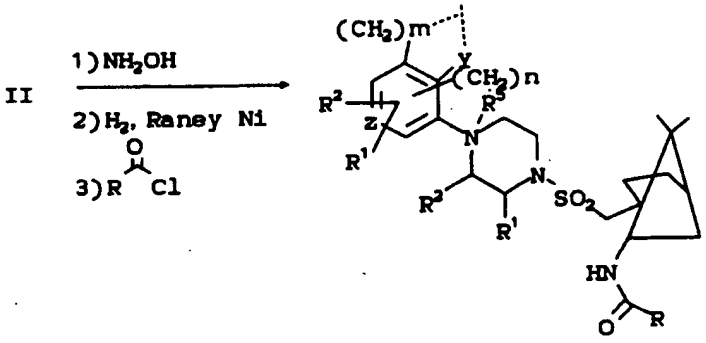
SCHEME 5



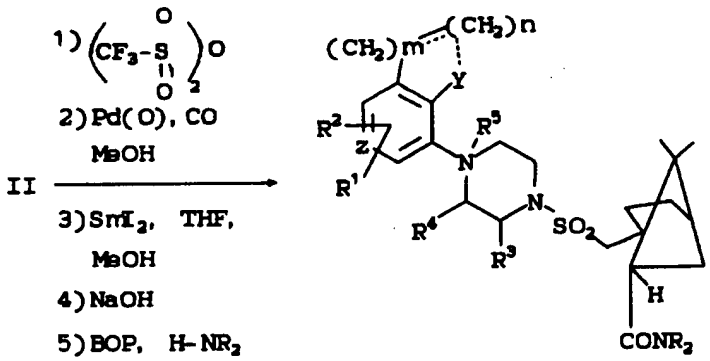
SCHEME 6



SCHEME 7



SCHEME 8



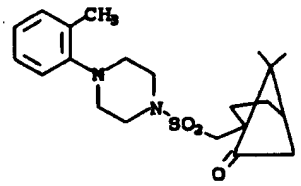
Abbreviations used in the Examples are as follows:

TEA	= triethylamine
DIEA	= diisopropylethylamine
BOP	= benzotriazolyloxytris(dimethylamino) phosphonium hexafluorophosphate
THF	= tetrahydrofuran
DMF	= dimethylformamide
LAH	= lithium aluminum hydride
TFA	= trifluoroacetic acid
HPLC Method A	= 15 min. linear gradient 95:5 A:B to 0:100 A:B A - H_2O containing 0.1% by vol. TFA B = CH_3CN containing 0.1% by vol. TFA 2.0 mL/min flow rate 12 cm C_{18} reverse phase column UV detection (215 nm)

TLC was performed on 20 cm plates coated with silica gel (250 microns) from Analtech.

Example 1

1-((7,7-DIMETHYL-2-OXO-BICYCLO(2.2.1)HEPTAN-1-YL) METHANESULFONYL)-4-(2-METHYLPHENYL)-PIPERAZINE



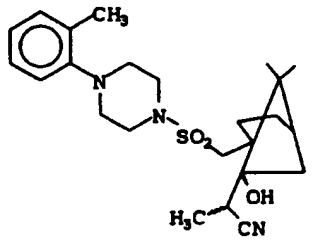
To a stirred, 0°C solution of 1-(o-tolyl)piperazine hydrochloride (50.0 g; 235 mmol) and TEA (83 mL; 590 mmol) in chloroform (1000 mL) was added (+)-10-camphorsulfonyl chloride (65.5 g; 260 mmol). The solution was stirred at 0°C for 1 h and then at ambient temperature for 3 h. The solution was extracted with 5% aqueous HCl (2 x 500 mL), water (500 mL), and saturated aqueous $NaHCO_3$ (2 x 500 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The resulting solid was r crystalliz d from methanol to giv th titl compound, mp 112-114°C (69 g; 75%).

anal: ($C_{21}H_{30}N_2O_3S$)			
calc.	C, 64.57;	H, 7.74;	N, 7.17
found	C, 64.52;	H, 7.68;	N, 6.99

TLC: R_f 0.49 (75:25 hexane/ethyl acetate)
HPLC (method A): retention time 10.33 min
FAB MS: m/z 391 (M^+ + H)
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.2 (m, 2H), 7.0 (m, 2H), 3.45 (m, 4H), 3.40 (d, J = 16 Hz, 1H), 3.0 (m, 4H), 2.57 (m, 1H), 2.40 (dt, Jd = 14 Hz, Jt = 3 Hz, 1H), 2.30 (s, 3H), 2.10 (m, 2H), 1.96 (d, J = 14 Hz, 1H), 1.67 (m, 1H), 1.44 (m, 1H), 1.18 (s, 3H), 0.91 (s, 3H)

Example 2

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-(1-CYANO)ETHYL-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYL PHENYL)PIPERAZINE:



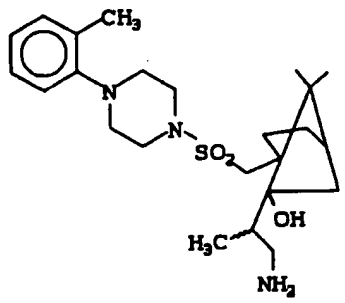
To a stirred, -78 °C solution of diisopropylamine (21.0 mL; 150 mmol) in THF (350 mL) was added n-butyllithium (60 mL of a 2.5 M solution in hexane; 150 mmol). The solution was warmed to 0 °C for 15 min, then cooled to -78°C. A solution of propionitrile (10.1 mL; 141 mmol) in THF (75 mL) was added dropwise, and the resulting solution was stirred at -78 °C for 45 min. A -78 °C solution of 1-((7,7-dimethyl-2-oxo-bicyclo-(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (50.0 g; 128 mmol) in THF (350 mL) was added via cannula, and the resulting solution was stirred at -78 °C for 5 min. A solution of 5:1 THF/water (100 mL) was added and the mixture was warmed to ambient temperature. The mixture was diluted with EtOAc (500 mL) and washed with 5% aqueous citric acid (2 x 500 mL), and brine (250 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure to give a foam. The major isomer by TLC was obtained by crystallization from ether, mp 163-165 °C.

anal: ($C_{24}H_{35}N_3O_3S$)			
calc.	C, 64.69;	H, 7.92;	N, 9.43
found	C, 64.72;	H, 7.99;	N, 9.35

TLC: R_f 0.31 (75:25 hexane/ethyl acetate)
HPLC (method A): retention time 10.20 min
FAB MS: m/z 446 (M^+ + H)
1H NMR (300 MHz, $CDCl_3$): δ 7.19 (m, 2H), 3.70 (d, J = 15 Hz, 1H), 3.68 (s, 1H), 3.49 (m, 4 H), 3.38 (d, J = 15 Hz, H), 2.75 (q, J = 7 Hz, 1H), 2.30 (s, 2H), 2.05 (m, 2H), 1.7-1.9 (m, 3H), 1.47 (d, J = 7 Hz, 3H), 1.41 (d, J = 12 Hz, 1H), 1.40 (s, 3H), 1.15 (s, 3H), 1.04 (m, 1H)

Example 3

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred, -78°C solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-(1-cyano)ethyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (25.0 g; 56.2 mmol) in THF (350 mL) was added dropwise a 1.0 M solution of LAH in THF (170 mL; 170 mmol). The resulting solution was stirred at -78°C for 1 h, and then warmed to 0°C for 3 h. Ether (300 mL) was added, followed by the slow dropwise addition of 5 M NaOH solution (35 mL). The resulting suspension was warmed to ambient temperature and stirred for 1 h. EtOAc (250 mL) was added and stirring was continued for 30 min. The solids were removed by filtration through Celite and washed with EtOAc. The filtrate sovents were removed under reduced pressure to give a foam. The title compound was obtained by crystallization from methanol, mp 172-174°C (17.2 g; 68%).

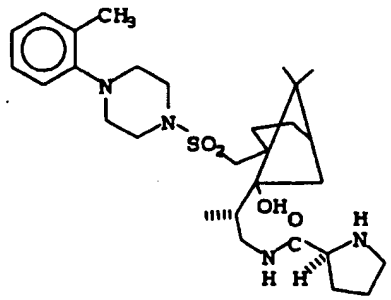
anal: ($C_{24}H_{39}N_3O_3S$)			
calc.	C, 64.11;	H, 8.74;	N, 9.35
found	C, 64.09;	H, 8.88;	N, 9.31

TLC: R_f 0.50 (95:5:0.5 $CHCl_3$/MeOH/NH_4OH)

HPLC (method A): retention time 9.80 min
FAB MS: m/z 450 (M^+ + H)
^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (m, 2H), 7.05 (m, 2H), 2.32 (s, 3H), 1.13 (d, J=6 Hz, 3H), 1.11 (s, 3H), 1.02 (s, 3H)

Example 4

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(L-PROLYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



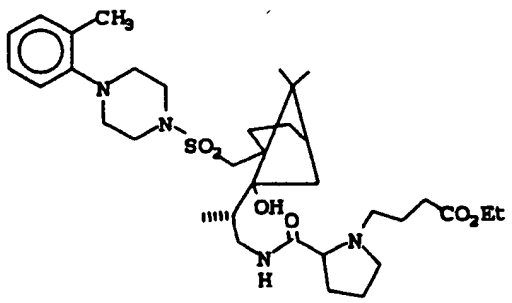
To a stirred solution of 1-((7,7-dimethyl-2- xo-hydroxy-2-endo-2-(1-amino)propyl-(2.2.1)bicycloh ptan-1-yl)-methanesulfonyl)-4-(2-methylphenyl) piperazin (2.00 g; 4.45 mmol) in DMF (30 mL) was added Nα-Fmoc-L-proline (1.58 g; 4.68 mmol), BOP (2.17 g; 4.90 mmol), and DIEA (1.71 mL; 9.80 mmol). After 16 h, diethylamine (6 mL) was added and the solution was stirred at ambient temperature for 3 h. The solvents were removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

anal: ($C_{29}H_{46}N_4O_4S$)			
calc.	C, 52.48;	H, 6.50;	N, 7.56
found	C, 52.46;	H, 6.50;	N, 7.69

1.7 TFA, 0.05 H_2O
TLC: R_f 0.45 (90:10:1 $CHCl_3$:MeOH:NH_4OH)
HPLC (method A): retention time 8.60 min
FAB MS: m/z 547 (M^+ + H)
^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (br t, 1H), 7.18 (m, 2H), 7.03 (m, 2H), 2.31 (s, 3H), 1.14 (s, 3H), 1.02 (s, 3H), 0.99 (d, J = 7 Hz, 3H)

Example 5

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(L-N-(ETHOXYCARBONYLPROPYL)PROLYL)AMINO)-PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL) PIPERAZINE:



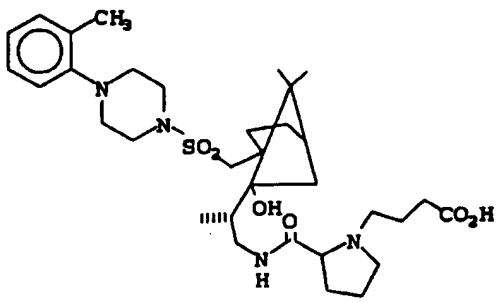
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(L-prolyl)amino)propyl-(2.2.1) bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl) piperazine (1.50 g; MW = 679; 2.21 mmol) in DMF (15 mL) was added ethyl 4-bromobutyrate (538 mg; 2.76 mmol), and DIEA (1.15 mL; 6.63 mmol). After 72 h at ambient temperature, the solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of the title compound was obtained as a lyophilized powder.

anal: ($C_{35}H_{56}N_4O_6S$)			
calc.	C, 51.99;	H, 6.48;	N, 6.17
found	C, 52.01;	H, 6.33;	N, 6.17

2.1 TFA, 0.1 H_2O
TLC: R_f 0.40 (95:5 $CHCl_3$:MeOH)
HPLC (method A): retention time 10.23 min
FAB MS: m/z 661 (M^+ + H)
^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (m, 1H), 7.20 (m, 2H), 7.08 (m, 2H), 2.35 (s, 3H), 1.25 (t, J = 6Hz, 3H), 1.14 (s, 3H), 1.03 (overlapping s and d, 6H)

Example 6

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(L-N-(3-CARBOXYPROPYL)PROLYL)AMINO) PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



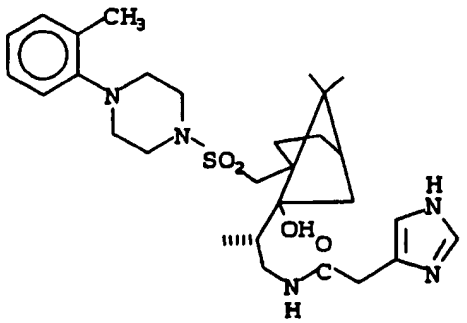
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(L-N-(ethoxycarbonylpropyl) prolyl)-amino)propyl-(2.2.1)bicycloheptan-1-yl) methanesulfonyl)-4-(2-methylphenyl)piperazine (1.00 g; MW = 909; 1.10 mmol) in THF (15 mL) was added 1 M NaOH solution (1.0 mL; 4.0 mmol) until a pH 10 solution persisted for 1 h. The solution was acidified to pH 7 by addition of citric acid and the solvents were removed under reduced pressure. The residue was dissolved in dichloromethane (75 mL) and washed with water (3 x 25 mL), dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The residue was lyophilized from dioxane-water to give the title compound as a white powder.

anal: ($C_{33}H_{52}N_4O_6S$)			
calc.	C, 59.78;	H, 8.25;	N, 6.94
found	C, 59.86;	H, 7.98;	N, 6.92

0.1 Na citrate, 1.65 dioxane
TLC: R_f (80:20:2 $CHCl_3$:MeOH:NH_4OH)
HPLC (method A): retention time 9.24 min
FAB MS: m/z 633 (M^+ + H)
^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (br s, 1H), 7.18 (m, 2H), 7.03 (m, 2H), 2.31 (s, 3H), 1.15 (s, 3H), 1.04 (s, 3H), 0.98 (d, J = 6 Hz, 3H)

Example 7

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(4(5)-IMIDAZOLYLACETYL)AMINO)PROPYL-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred solution of 1-((7,7-dimethyl-2- xo-hydroxy-2-endo-2-(1-amino)propyl-(2.2.1)bicyclo-heptan -1-yl)-methanesulfonyl)-4-(2-methylphenyl)piperazine (1.50 g; 3.34 mmol) in DMF (15 mL) was added 4(5)-

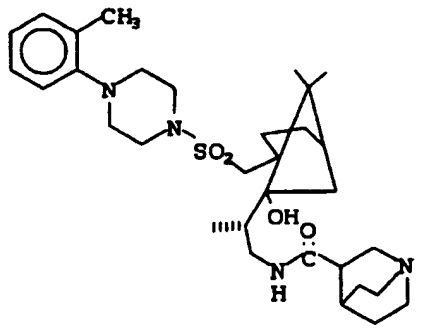
imidazol acetic acid hydrochloride (679 mg; 4.18 mmol), BOP (1.85 g; 4.18 mmol), and DIEA (2.18 mL; 12.5 mmol). Aft r 16 h, the solv nt was removed under r duced pr ssure. The residu was dissolv d in EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 x 50 mL) and water (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 92:8:0.8 as eluant. The title comound crystallized from EtOAc, mp 159-163°C.

anal: ($C_{29}H_{43}N_5O_4S$)			
calc.	C, 62.45;	H, 7.77;	N, 12.56
found	C, 62.88;	H, 7.68;	N, 12.79

TLC: R_f 0.4 (90:10:1 $CHCl_3$/MeOH/NH_4OH)
HPLC (method A): retention time 8.72 min
FAB MS: m/z 558 (M^+ + H)
^1H NMR ($CDCl_3$): δ 7.57 (s, 1H), 7.2 (m, 3H), 7.0 (m, 2H), 6.88 (s, 1H), 3.55 (m, 2H), 3.4 (m, 5H), 2.95 (m, 4H), 2.87 (d, J = 15 Hz, 1H), 2.31 (s, 3H), 1.71 (t, J = 4 Hz, 1H), 1.52 (d, J = 13 Hz, 1H), 1.15 (s, 3H), 1.03 (s, 3H), 0.97 (d, J = 6 Hz, 3H)

Example 8

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-QUINUCLIDIN-3-YL-CARBONYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



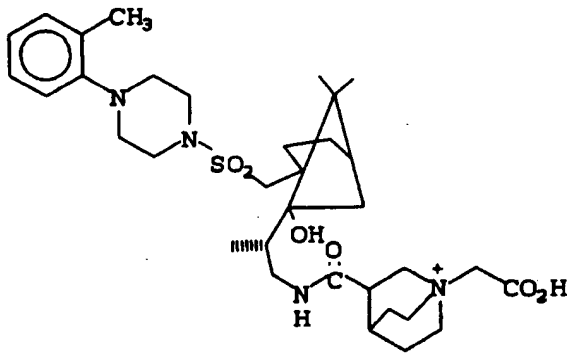
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-amino)propyl-(2.2.1.)bicycloheptan-1-yl)-methanesulfonyl)-4-(2-methylphenyl) piperazine (2.00 g; 4.45 mmol) in DMF (50 mL) was added quinuclidine-3-carboxylic acid hydrochloride (938 mg; 4.90 mmol, BOP (2.17 g; 4.90 mmol), and DIEA (2.56 mL; 14.7 mmol). After 16 h, the solvent was removed under reduced pressure. The residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 1% acetic acid. The acetate salt of the title compound (1:1 mixture of diastereomers) was obtained as a lyophilized powder.

anal: ($C_{32}H_{50}N_4O_4S$)			
calc.	C, 60.39;	H, 8.58;	N, 8.39
found	C, 60.41;	H, 8.19;	N, 8.58

0.8 CH_3CO_2H, 1.85 H_2O
TLC: R_f 0.65 (80:20:2 $CHCl_3$:MeOH:NH_4OH)
HPLC (m thod A): retention time 8.68 min
FAB MS: m/z 587 (M^+ + H)
^1H NMR (300 MHz, $CDCl_3$): δ 7.19 (m, 2H), 7.02 (m, 2H), 2.30 (s, 3H), 1.16 (s, 3H), 1.03 (overlapping s and d, 6H)

Example 9

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(1-CARBOXYMETHYLQUINUCLIDIN-3-YL-CARBOXYL)-AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-PIPERAZINE:



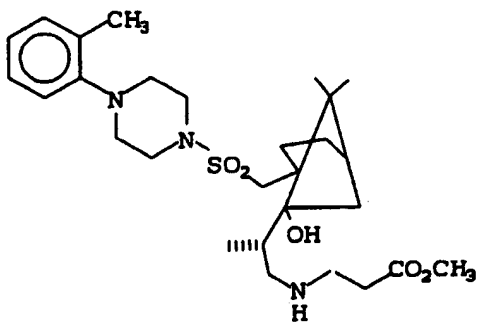
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(quinuclidin-3-yl-carbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.50 g; MW = 668; 2.25 mmol) in DMF (30 mL) was added iodoacetic acid (543 mg; 2.92 mmol) and DIEA (0.43 mL; 2.48 mmol). After 16 h, TLC showed complete consumption of starting material. The solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 1% acetic acid. The title compound, as a 1:1 mixture of diastereomers, was obtained as a lyophilized powder.

anal: ($C_{34}H_{52}N_4O_4S$)			
calc.	C, 60.52;	H, 8.18;	N, 8.04
found	C, 60.52;	H, 7.98;	N, 8.15

0.55 CH_3CO_2H, 0.95 H_2O
TLC: R_f 0.20 (80:20:2 $CHCl_3$:MeOH:NH_4OH)
HPLC (method A): retention time 8.73 min
FAB MS: m/z 647 (M^+ + H)
^1H NMR (TFA salt; 400 MHz, $CDCl_3$): δ 7.46 (br s, 1H), 7.19 (m, 2H), 7.02 (m, 2H), 2.30 (s, 3H), 1.13 (s, 3H), 1.02 (s, 3H), 0.98 (d, J = 6 Hz, 3H)

Example 10

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(2-METHOXYCARBONYLETHYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



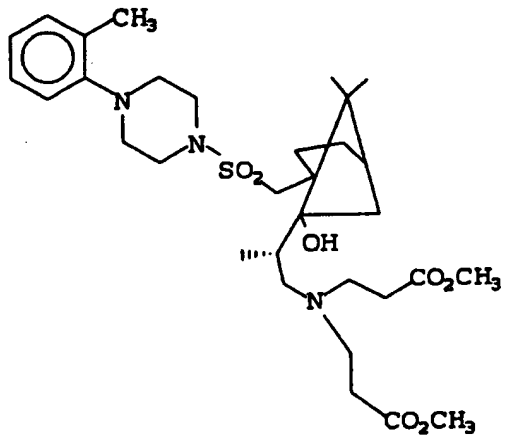
To a stirr d solution of 1-((7,7-dimethyl-2-exo-hydroxy-2- ndo-2-(1-amino)propyl-(2.2.1)bicycloheptan-1-yl)-methanesulfonyl)-4-(2-methylph nyl)piperazin (100 mg; 0.22 mmol) in 1:1 DMF-M OH (3 mL) was added methyl acrylate (0.020 mL; 0.22 mmol). Aft r 16 h, the solv nts w re removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of the title compound was obtained as a lyophilized powder.

anal: ($C_{28}H_{45}N_3O_5S$)			
calc.	C, 53.03;	H 6.88;	N, 6.06
found	C, 53.01;	H, 6.90;	N, 6.01

1.3 TFA, 0.5 H_2O
TLC: R_f 0.35 (95:5 $CHCl_3$:MeOH)
HPLC (method A): retention time 9.04 min
FAB MS: m/z 536 (M^+ + H)
^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (m, 2H), 7.03 (m, 2H), 3.72 (s, 3H), 2.32 (s, 3H), 1.19 (d, J=6 Hz, 3H), 1.15 (s, 3H), 0.98 (s, 3H)

EXAMPLE 11

1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-bis-(2-methoxycarbonylethyl)amino)propyl-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine



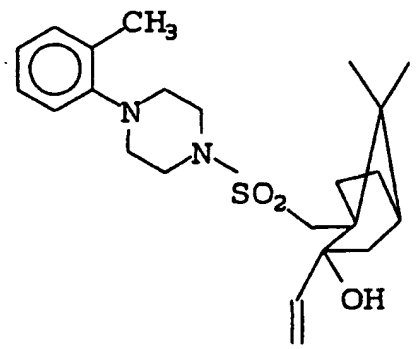
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-amino)-propyl-(2.2.1)bicycloheptan-1-yl)-methanesulfonyl)-4-(2-methylphenyl) piperazine (100 mg; 0.22 mmol) in 1:1 DMF-MeOH (3 mL) was added methyl acrylate (0.080 mL);0.89 mmol). After 16 h, the solvents were removed under reduced pressure and the residue was purified by pressurized silica gel chromatography using 3:1 hexane-ethyl acetate as eluant. The title compound was obtained as a foam from hexane.

Anal: ($C_{32}H_{51}N_3O_7S$)			
Calc:	C 61.81,	H 8.27,	N 6.76
Found:	C 61.55,	H 8.13,	N 6.55

TLC: R_f 0.40 (1:3 EtOAc:hexan s)
HPLC (method A): rentention time 9.71 min
FAB MS: m/z 622 (M^+ + H)
^1H NMR (300 MHz, CDCl3): δ 7.19 (m, 2H), 7.02 (m, 2H), 3.66 (s, 6H), 2.31 (s, 3H), 1.13 (s, 3H), 1.00 (overlapping a and d, 6H)

EXAMPLE 12

1-((7,7-dimethyl-2-exo-hydroxy-2-endo-ethenyl-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine



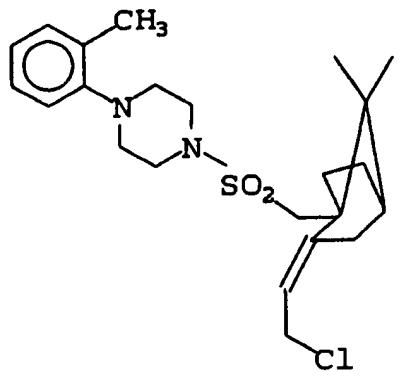
To a -78°C stirred 1.0 M solution of vinyl magnesium chloride in THF (25 mL; 25 mmol) was added a -78°C solution of 1-((7,7-dimethyl-2-oxo-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl) piperazine (5.00 g; 12.8 mmol) in THF (100 mL) via cannula. The resulting solution was stirred under arogn overnight, allowing the cooling bath to warm to ambient temperature. The reaction was quenched by addition of 2% aqueous HCl (50 ML), and the mixture was partitioned between ethyl acetate and water. The organic phase was washed with aqurous $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The solvents were removed under reduced pressure and the residue was purified by pressurized silica gel chromatography using 4:1 hexane-ethyl acetate as eluant. The title compound was obtained as a white foam from ether.

Anal: ($C_{23}H_{34}N_2O_3S$) 0.06 H_2O			
Calc:	C 65.82,	H 8.19,	N 6.67
Found:	C 65.99,	H 8.42,	N 6.63

TLC: R_f 0.36 (1:5 EtOAc:hexanes)
HPLC (method A): rentention time 11.41 min
FAB MS: m/z 419 (M^+ + H)
^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 2H), 7.02 (m, 2H), 6.48 (dd, 1H), 5.30 (d, 1H), 5.17 (d, 1H), 2.32 (s, 3H), 1.22 (s, 3H), 0.94 (s, 3H).

EXAMPLE 13

1-((7,7-dimethyl-2-(2-chloro)ethylidine-bicyclo(2.2.1)h ptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)-piperazine



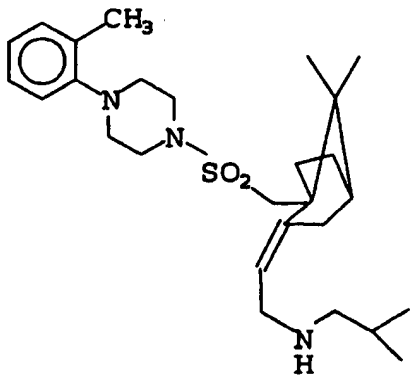
To a 0°C stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-ethenyl-(2.2.1)bicycloheptan-1-yl) methanesulfonyl)-4-(2-methylphenyl)piperazine (2.90 g; 6.94 mmol) in THF (100 mL) was added triethylamine (1.50 mL; 10.7 mmol) and DMF (0.58 mL;7.5 mmol). Thionyl chloride (0.66 mL; 9.1 mmol) was added dropwise, and the resulting solution was stirred for 18 h, allowing the cooling bath to warm ambient temperature. The solvents were removed under reduced pressure and the residue was dissolved in theyl acetate (150 mL) and washed with 5% aqueous HCl (75 mL), water (75 mL) and aqueous $NaHCO_3$ (100 mL). The organic phase was dried ($MgSO_4$). filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 4:1 hexane-ethyl acetate as eluant. The title compound was obtained as a white foam.

Anal: ($C_{23}H_{33}ClN_2O_2S$) 0.6 H_2O			
Calc:	C 65.82,	H 8.19,	N 6.67
Found:	C 65.99,	H 8.42,	N 6.63

^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 2H), 7.03 (m, 2H), 5.87 (m, 1H), 2.32 (s, 3H), 1.00 (s, 3H), 0.82 (s, 3H)

EXAMPLE 14

1-((7,7-dimethyl-2-(2-isobutylamino)ethylidine-bicyclo (2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methyl-phenyl) piperazine



To a stirred solution of 1-((7,7-dim thyl-2-(2-chloro) ethylidin -(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylph nyl)peperazine (200 mg; 0.46 mmol) in MeOH (2 mL) was add d isobutylamin (0.5 mL; 5 mmol). After being stirred fro 18 h, the solvents were removed under reduc d pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of the title compound was obtained as a lyophilized powder.

TLC: R_f 0.30 (95:5:0.5 $CHCl_3$:MeOH:NH_4OH)

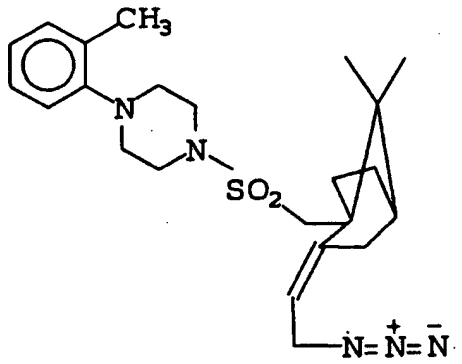
HPLC (method A): rentention time 9.78 min

FAB MS: m/z 474 (M^+ + H)

^1H NMR (400 MHz, CD_3OD): δ 7.20 (m, 3H), 7.03 (t, 1H), 5.78 (m, 1H), 2.35 (s, 3H), 1.13 (d, J = 7 Hz, 6H), 1.12 (s, 3H), 0.88 (s, 3H)

EXAMPLE 15

1-((7,7-dimethyl-2-(2-azido)ethylidine-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)-piperazine



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-(2-chloro)ethylidine-(2.2.1)bicycloheptan-1-yl)-methanesulfonyl)-4-(2-methylphenyl) piperazine (3.58 g;8.19 mmol) in DMSO (50 mL) and THF (45 mL) was added a solution of sodium azide (5.3 g; 82 mmol) in water (20 mL). After 24 h, the solvents were removed under reduced pressure, the residue was suspended in dichloromethane (100 mL) and washed with water (3 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give a solid.

Anal: ($C_{23}H_{33}N_5O_2S$)			
Calc:	C 62.27,	H 7.50,	N 15.79
Found:	C 62.41,	H 7.54,	N 15.60

TLC: R_f 0.75 (70:30 hexane-ethylacatate)

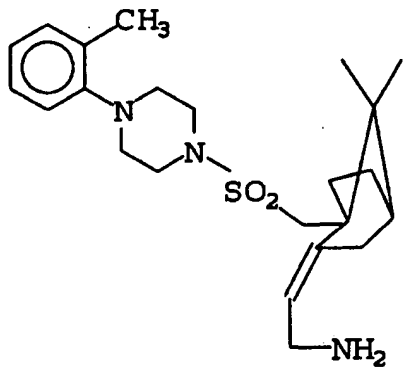
HPLC (method A): rentention time 12.50 min

FAB MS: m/z 444 (M^+ + H)

^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (m, 2H), 7.02 (m, 2H), 5.79 (m, 1H), 2.32 (s, 3H), 0.85 (s, 3H)

EXAMPLE 16

1-((7,7-dimethyl-2-(2-amino)ethylidinebicyclo(2.2.1)h ptan-1-yl)m thanesulfonyl)-4-(2-methylphenyl)-piperazine



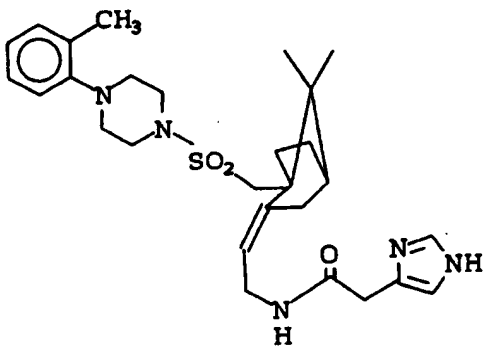
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-(2-azido)ethylidine-(2.2.1)bicycloheptan-1-yl)-methanesulfonyl)-4-(2-methylphenyl)piperazine (3.85 g; 8.69 mmol) in THF (150 mL) and water (3 mL) was added triphenylphosphine (2.50 g; 9.56 mmol). After 14 h, the solvents were removed under reduced pressure. The residue was dissolved in ethyl acetate (150 mL) and extracted with 5% aqueous HCl (3 x 75 mL). The combined acid extracts were washed wtih ethyl acetate (50 mL) and then made basic by adding solid sodium hydroxide to pH 12. The aqueous phase was extracted with chloroform (3 x 50 mL) and the combined organic phases were dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 99:1 to 85:15 chloroform-methanol. The title compound was obtained as a solid.

Anal: ($C_{23}H_{35}N_3O_2S$) 0.5 H_2O			
Calc:	C 64.75;	H 8.51;	N 9.85;
Found:	C 64.59;	H 7.51;	N 9.71

TLC: R_f 0.56 (95:5:0.5 $CHCl_3$-MeOH-NH_4OH)
HPLC (method A): retention time 10.38 min
FAB MS: m/z 418 (M^+ + H)

EXAMPLE 17

1-((7,7-dimethyl-2-(2-(4(5)-imidazolylacety)amino) ethylidine-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine



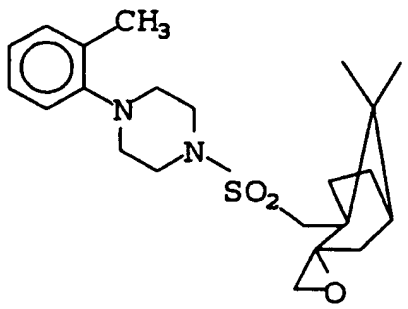
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-(2-amino)ethylidin -(2.2.1)bicycloheptan-1-yl)-methanesulfonyl)-4-(2-methylphenyl)piperazin (0.20 g; 0.48 mmol) in DMF (5 mL) was add d BOP (265 mg; 0.60 mmol), 4-imidazoleacetic acid hydrochloride (115 mg; 0.72 mmol) and DIEA (0.38 mL; 2.2 mmol). After 14 h, the solvents were removed under reduced pressure, the residue was suspended in ethyl acetate (50 mL) and washed with aqueous $NaHCO_3$ (2 x 25 mL) and water (2 x 25 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The residue was purified by preparative reverse phase HPCL using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of the title compound was obtained as a lyophilized powder.

Anal: ($C_{28}H_{39}N_5O_3S$); 0.5 H_2O; 2.0 TFA;			
Calc:	C 50.38;	H 5.55;	N 9.18
Found:	C 50.40;	H 5.55;	N 9.40

TLC: R_f 0.42 (95:5:0.5 $CHCl_3$-MeOH-NH_4OH)
HPLC (method A): retention time 8.76 min.
FAB MS: m/z 526 (M^+ + H)
^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.58 (br m, 1H), 7.22 (m, 3H), 7.10 (m, 2H), 5.57 (br t, 1H), 2.37 (s, 3H), 0.97 (s, 3H), 0.76 (s, 3H)

Example 18

1-((7,7-DIMETHYL-2-SPIRO-EPOXY-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred 0 °C suspension of trimethylsulfoxonium iodide (6.78 g; 30.8 mmol) in THF (100 mL) was added n-butyllithium (11.1 mL of a 2.5 M solution in hexane; 27.7 mmol). After 4 h at 0°C, a solution of 1-((7,7-dimethyl-2-oxo-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (8.00 g; 20.5 mmol) in THF (50 mL). The resulting solution was stirred at 0 °C for 2 h, and then at ambient temperature for 18 h. The solvents were removed under reduced pressure, the residue was dissolved in ethyl acetate (150 mL) and washed with water (2 x 50 mL). The organic phase was dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The resulting solid was recrystallized from ether to give the title compound. as white needles.

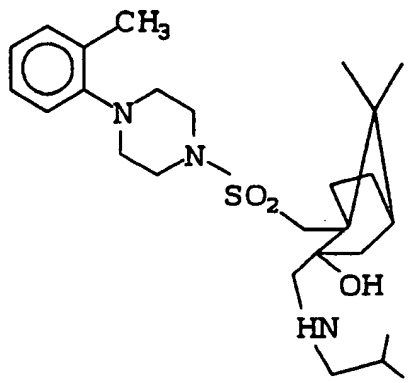
anal: ($C_{22}H_{32}N_2O_2S$)			
calc.	C, 65.31;	H, 7.97;	N, 6.92
found	C, 65.09;	H, 7.99;	N, 6.86

0.5 H_2O
TLC: R_f 0.62 (4:1 hexane-ethyl acetate)
HPLC (method A): retention time 11.50 min
FAB MS: m/z 405 (M^+ + H)
^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (m, 2H), 7.02 (m, 2H), 3.20 (d, J=5.4 Hz, 1H), 2.70 (d, J=5.4 Hz, 1H),

2.30 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H)

Example 19

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-ISOBUTYLAMINOMETHYL-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



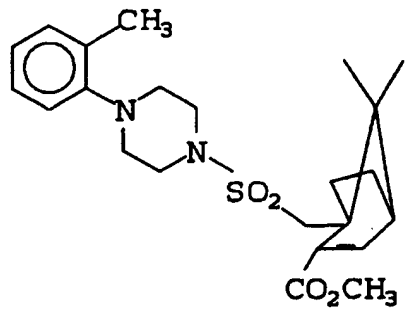
To a stirred solution of 1-((7,7-dimethyl-2-(spiro-epoxy)-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (200 mg; 0.495 mmol) in MeOH (3 mL) was added isobutylamine (0.5 mL; 5 mmol). After being stirred for 18 h, the solvents were removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using 98:2:0.2 chloroform-methanol-NH_4OH as eluant. The product was dissolved in methanol and to it was added several drops of 5% aqueous HCl. The solvents were removed under reduced pressure and the residue was triturated in ether to give the hydrochloride salt of the title compound as a white powder.

anal: ($C_{26}H_{43}N_3O_3S$)			
calc.	C, 57.00;	H, 8.76;	N, 7.67
found	C, 57.03;	H, 8.84;	N, 7.61

1.0 HCl, 1.8 H_2O
TLC (free base): R_f 0.20 (3:1 hexane-ethyl acetate)
HPLC (method A): retention time 9.54 min
FAB MS: m/z 478 (M^+ + H)
^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (m, 2H), 7.02 (m, 2H), 2.30 (s, 3H), 1.10 (s, 3H), 0.95 (s, 3H), 0.90 (two doublets, 6H)

Example 20

1-((7,7-DIMETHYL-2-METHOXYCARBONYL-BICYCLO (2.2.1)HEPT-2-EN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



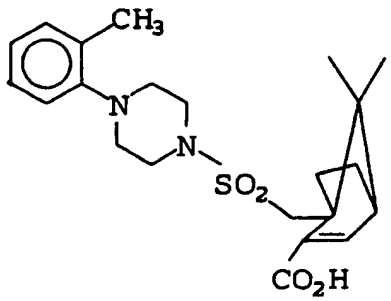
To a stirred, 0°C solution of 1-((7,7-dimethyl-2-oxo-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methyl phenyl)piperazine (10.0 g; 25.6 mmol) in dichloromethane (500 mL) was added 2,6-di-t-butyl-4-methyl-pyridine (7.8 g; 38 mmol) and trifluoromethanesulfonic anhydride (5.4 mL; 32 mmol). The cooling bath was removed and the solution was stirred for 18 h. The mixture was filtered and the filtrate was washed with 5% aqueous HCl (2 x 100 mL), water (100 mL), and aqueous $NaHCO_3$ (2 x 100 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 9:1 hexane-ethyl acetate as eluant. The enol triflate product was obtained as a white foam and used as such in the next step. To a stirred solution of 1-((7,7-dimethyl-2-trifluoro-methanesulfonyloxy-bicyclo(2.2.1)hep-2-en-1-yl)methanesulfonyl)-4-(2-methylphenyl)-piperazine (10.5 g; 20.1 mmol) in 1:1 DMF-MeOH (150 mL) was added triethylamine (5.9 mL; 43 mmol), triphenylphosphine (317 mg; 1.21 mmol), and palladium(II)acetate (135 mg; 0.603 mmol). Carbon monoxide gas was bubbled through the solution for 15 min, and the reaction was kept under atmospheric pressure of CO for 18 h. The solvents were removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using 9:1 hexane-ethyl acetate as eluant. The title compound was obtained as a white foam from hexane.

anal: ($C_{23}H_{32}N_2O_4S$)			
calc.	C, 62.14;	H, 7.50;	N 6.30
found	C, 61.65;	H, 7.17;	N, 6.12

0.67 H_2O
TLC: R_f 0.36 (1:5 EtOAc:hexanes)
HPLC (method A): retention time 11.34 min
FAB MS: m/z 433 (M^+ + H)
^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 2H), 7.03 (m, 2H), 6.88 (d, J = 3 Hz, 1H), 3.72 (s, 3H), 2.33 (s, 3H), 1.09 (s, 3H), 1.01 (s, 3H)

Example 21

1-((7,7-DIMETHYL-2-CARBOXY-BICYCLO(2.2.1) HEPT-2-EN-1-YL)METHANESULFONYL)-4-(2-METHYL-PHENYL)PIPERAZINE



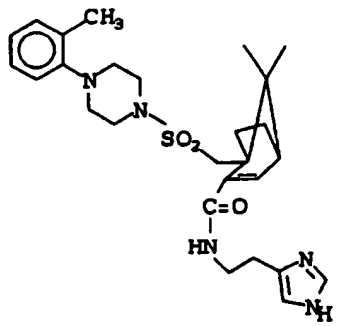
To a stirred solution of 1-((7,7-dimethyl-2-methoxycarbonyl-bicyclo(2.2.1)hept-2-en-1-yl)methanesulfonyl) -4-(2-methylphenyl)piperazine (1.0 g; 2.3 mmol) in MeOH (10 mL) was added a solution of 4 M aqueous KOH (2.0 mL; 8.0 mmol). After 18 h, the reaction was brought to pH 1 with 5% aqueous HCl, and the solvents were removed under reduced pressure. The residue was taken up in chloroform (50 mL) and washed with water (25 mL). The organic phase was dried (MgSO4), filtered, and the solvent was removed under reduced pressure to give the hydrochloride salt of the title compound as a white foam.

anal: ($C_{22}H_{30}N_2O_4S$)			
calc.	C, 57.51;	H, 6.91;	N, 6.10
found	C, 57.40;	H, 6.87;	N, 6.01

1.0 HCl, 0.25 H_2O
TLC: R_f 0.59 (92:8:0.1 $CHCl_3$ MeOH:HOAc)
HPLC (method A): retention time 9.77 min
FAB MS: m/z 419 (M^+ + H)
^1H NMR (400 MHz, CD_3OD): δ 7.30 (m, 3H), 7.20 (t, 1H), 6.89 (d, J = 3 Hz, 1H), 2.43 (s, 3H), 1.11 (s, 3H), 1.00 (s, 3H)

Example 22

1-((7,7-DIMETHYL-2-(4-IMIDAZOLYL)ETHYLAMINOCARBONYL-BICYCLO(2.2.1)HEPT-2-EN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred solution of 1-((7,7-dimethyl-2-carboxy-bicyclo(2.2.1)hept-2-en-1-yl)methan sulfonyl)-4-(2-m thyl-phenyl)piperazine (100 mg; FW = 460; 0.22 mmol) in DMF (5 mL) was added histamine (30 mg; 0.27 mmol), BOP (115 mg; 0.25 mmol) and DIEA (0.12 mL; 0.69 mmol). After 18 h, the solvent was removed under

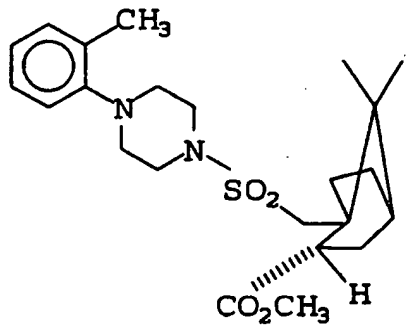
reduced pressure, the residu was purified by preparativ reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. Th TFA salt of the title compound was obtain d as a lyophiliz d powd r.

anal: ($C_{27}H_{37}N_5O_3S$)			
calc.	C, 49.35;	H, 5.31;	N, 9.22
found	C, 49.25;	H, 5.39;	N, 9.20

2.1 TFA, 0.45 H_2O
HPLC (method A): retention time 8.16 min
FAB MS: m/z 512 (M^+ + H)
^{1}H NMR (300 MHz, CD_3OD): δ 8.80 (s, 1H), 7.40 (s, 1H), 7.18 (m, 2H), 7.05 (d, 1H), 6.99 (t, 1H), 6.41 (d, J = 3 Hz, 1H), 2.31 (s, 3H), 1.08 (s, 3H), 0.98 (s, 3H)

Example 23

1-((7,7-DIMETHYL-2-ENDO-METHOXYCARBONYL-BICYCLO (2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



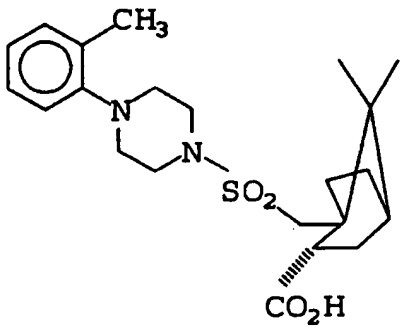
To a stirred, -78°C solution of 1-((7,7-dimethyl-2-methoxycarbonyl-bicyclo(2.2.1)hept-2-en-1-yl)-methanesulfonyl)-4-(2-methylphenyl)piperazine (3.0 g; 6.9 mmol) in 2:1 THF-MeOH (50 mL) was added a solution of 0.1 M samarium(II) iodide in THF (250.0 mL; 25.0 mmol). After 1 h, the reaction was warmed to ambient temperature and stirred for another 1 h. The solvents were removed under reduced pressure and the residue was partitioned between ethyl acetate (100 mL) and water (50 mL). The layers were separated and the organic phase was washed with water (50 mL), dried ($MgSO_4$), filtered, and evaporated to dryness under reduced pressure. By ^{1}H NMR analysis, a 6:1 ratio of endo:exo products was obtained. The major, lower R_f isomer (endo) was obtained in pure form by pressurized silica gel column chromatography using a gradient elution of 98:2 to 95:5 hexane-ethyl acetate, followed by crystallization from ethyl acetate. The title compound was obtained as white needles.

anal: ($C_{23}H_{34}N_2O_4S$)			
calc.	C, 63.56;	H, 7.89;	N, 6.45
found	C, 63.31;	H, 7.83;	N, 6.43

TLC: R_f 0.44 (1:5 EtOAc:hexanes)
HPLC (method A): retention time 11.75 min
FAB MS: m/z 435 (M^+ + H)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 2H), 7.05 (m, 2H), 3.72 (s, 3H), 3.29 (ddd, 1H), 2.34 (s, 3H), 1.13 (s, 3H), 1.06 (s, 3H)

Example 24

1-((7,7-DIMETHYL-2-ENDO-CARBOXY-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



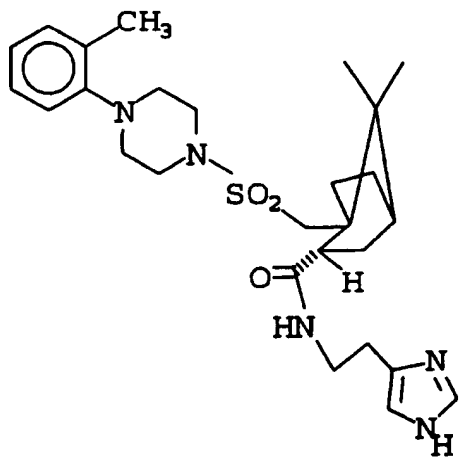
To a stirred solution of 1-((7,7-dimethyl-2-endo-methoxycarbonyl-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.0 g; 2.3 mmol) in THF (10 mL) was added a solution of 4 M aqueous NaOH (1.5 mL; 6.0 mmol). The reaction was heated to reflux for 72 h, cooled, and brought to pH 1 with 5% aqueous HCl. The solvents were removed under reduced pressure and the residue was partitioned between chloroform and water. The organic phase was separated and washed with water, dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The title compound was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The title compound was obtained as a lyophilized powder.

anal: ($C_{22}H_{32}N_2O_4S$)			
calc.	C, 51.92;	H, 5.99;	N, 4.94
found	C, 51.92;	H, 5.95;	N, 5.17

1.25 TFA, 0.2 H_2O
TLC: R_f 0.22 (95:5:0.5 $CHCl_3$:MeOH:NH_4OH)
HPLC (method A): retention time 10.67 min
FAB MS: m/z 421 (M^+ + H)
^1H NMR (300 MHz, CD_3OD): δ 7.18 (m, 2H), 7.05 (d, 1H), 6.98 (t, 1H), 2.30 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H)

Example 25

1-((7,7-DIMETHYL-2-ENDO-(4-IMIDAZOLYL)ETHYLAMINOCARBONYL-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



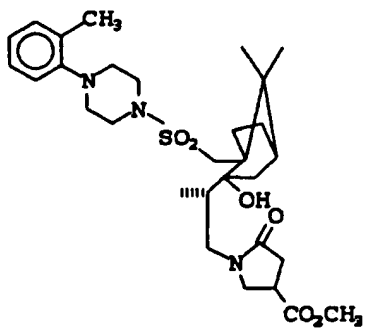
To a stirred solution of 1-((7,7-dimethyl-2-endo-carboxy-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (100 mg; 0.238 mmol) in DMF (5 mL) was histamine (35 mg; 0.32 mmol), BOP (142 mg; 0.321 mmol), and DIEA (0.13 mL; 0.75 mmol). After 18 h, the solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

anal: ($C_{27}H_{39}N_5O_3S$)			
calc.	C, 46 66;	H, 5.58;	N, 8.58
found	C, 46.63;	H, 5.23;	N, 8.97

2.35 TFA, 1.9 H_2O
HPLC (method A): retention time 8.99 min
FAB MS: m/z 514 (M^+ + H)
^1H NMR (300 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.1-7.3 (m, 5H), 2.39 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H)

Example 26

TWO ISOMERS OF 1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(3-METHOXYCARBONYL)-2-PYRROLIDINON-1-YL) PROPYLBICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYL-PHENYL)PIPERAZINE



To a stirred solution of 1-((7,7-dimethyl-2- xo-hydroxy-2-endo-2-(1-amino)propyl-(2.2.1)bicycloheptan-1-yl)-methan sulfonyl)-4-(2-m thylph nyl)pip razine (250 mg; 0.557 mmol) in m thanol (3 mL) was added dimethyl itaconate (200 mg; 1.27 mmol). The reaction was heated to reflux for 18 h. The solvent was removed under reduced pressure and the redidue was purified by pressurized silica gel column chromatography using 35:65 hexane-ethyl acetate as eluant. The products were obtained as white foams.

Isomer 1:

anal: ($C_{30}H_{45}N_3O_6S$)			
calc.	C, 62.58;	H, 7.88;	N, 7.30
found	C, 62.58;	H, 8.03;	N, 6.95

TLC: R_f 0.34 (35:65 heaxane-ethyl acetate)
HPLC (method A): retention time 10.23 min
FAB MS: m/z 576 (M^+ + H)
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (m, 2H), 7.01 (m, 2H), 3.76 (s, 3H), 2.32 (s, 3H), 1.15 (s, 3H), 1.03 (s, 3H), 0.95 (d, J = 6 Hz, 3H)

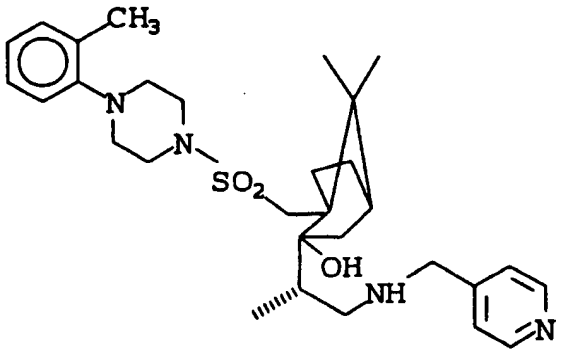
Isomer 2:

anal: ($C_{30}H_{45}N_3O_6S$)			
calc.	C, 62.58;	H, 7.88;	N, 7.30
found	c, 62.43;	H, 8.07;	N, 6.95

TLC: R_f 0.23 (35:65 heaxane-ethyl acetate)
HPLC (method A): retention time 10.24 min
FAB MS: m/z 576 (M^+ + H)
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (m, 2H), 7.03 (m, 2H), 3.74 (s, 3H), 2.32 (s, 3H), 1.15 (s, 3H), 1.03 (s, 3H), 0.95 (d, J = 6 Hz, 3H)

Example 27

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(4-PYRIDINYL)METHYLAMINO)PROPYL-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-amino)propyl-(2.2.1)bicyclo-heptan-1-yl)-methanesulfonyl)-4-(2-methylphenyl) piperazine (50 mg; 0.11 mmol) in DMF (2 mL) was add d 4-chloromethylpyridine hydrochloride (18 mg; 0.11 mmol) and potassium carbonate (50 mg; 0.36 mmol). The reaction was h at d to 80°C 18 h. The solvent was r mov d und r reduc d pr ssure and the residue was

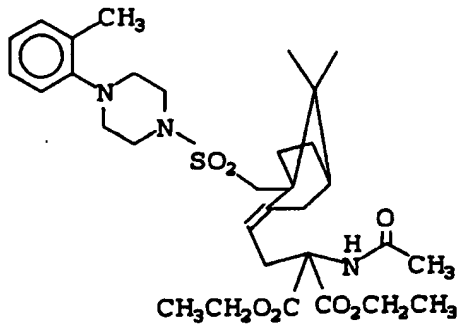
purified by preparativ reverse phas HPLC using an ac tonitril -water gradi nt containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

anal: ($C_{30}H_{44}N_4O_3S$)			
calc.	C, 52.07;	H, 5.89;	N, 7.06
found	C, 52.06;	H, 5.86;	N, 7.20

2.2 TFA, 0.1 H_2O
TLC: R_f 0.X
HPLC (method A): retention time 8.15 min
FAB MS: m/z 541 (M^+ + H)
^1H NMR (300 MHz, $CDCl_3$): δ 8.72 (br s, 2H), 7.85 (br s, 2H), 7.20 (m, 2H), 7.03 (m, 2H), 4.27 (AB quartet, 2H), 2.31 (s, 3H), 1.14 (s, 3H), 0.95 (overlapping s and d, 6H)

Example 28

1-((7,7-DIMETHYL-2-(3-ACETAMIDO-3,3'-DI(ETHOXYCARBONYL))PROPYLIDINE-BICYCLO(2.2.1)HEPTAN-1-YL) METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



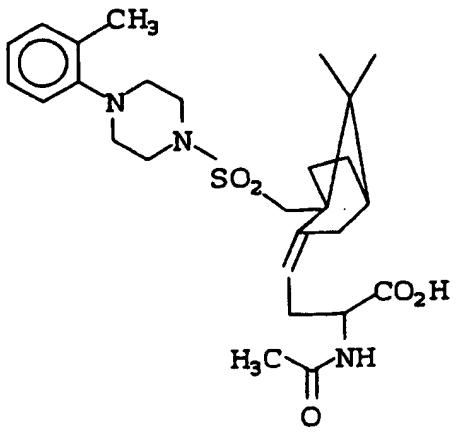
To a stirred solution of diethyl acetamidomalonate (0.69 g; 3.2 mmol) in DMF (20 mL) was added NaH (125 mg of a 60% dispersion in mineral oil; 3.13 mmol). After 30 min, 1-((7,7-dimethyl-2-(2-chloro)ethylidine-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.35 g; 0.80 mmol) was added and the mixture was warmed to 50 °C for 3 h. The mixture was cooled and acetic acid (1.5 mL) was added. The solvents were removed under reduced pressure, the residue was dissolved in ethyl acetate (75 mL) and washed with water (3 x 25 mL). The organic phase was dried, filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 2:1 hexane-ethyl acetate as eluant. The title compound was obtained as a white foam.

anal: ($C_{32}H_{47}N_3O_7S$)			
calc.	C, 62.32;	H, 7.51;	N, 6.81
found	C, 61.96;	H, 7.71;	N, 6.55

TLC: R_f 0.36 (95:5:0.5 $CHCl_3$:MeOH:NH_4OH)
HPLC (method A): retention time 11.54 min
FAB MS: m/z 618 (M^+ + H)
^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 2H), 7.03 (m, 2H), 6.78 (s, 1H), 5.38 (br t, 1H), 4.22 (m, 4H), 2.32 (s, 3H), 2.00 (s, 3H), 1.27 (t, J = 7 Hz, 3H), 1.24 (t, J = 7 Hz, 3H), 0.97 (s, 3H), 0.78 (s, 3H)

Example 29

1-((7,7-DIMETHYL-2-(3-ACETAMIDO-3-CARBOXY) PROPYLIDINE-BICYCLO(2.2.1)HEPTAN-1-YL) METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE:



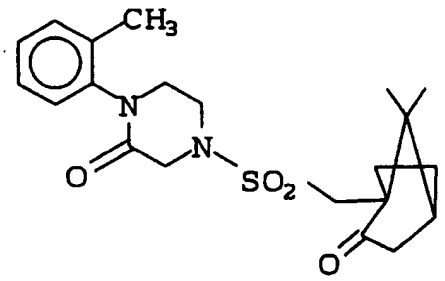
To a stirred solution of 1-((7,7-dimethyl-2-(3-acetamido-3,3'-di(ethoxycarbonyl))propylidine-(2.2.1) bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.10 g; 0.16 mmol) in ethanol (2 mL) was added a solution of 2 M NaOH (0.30 mL; 0.60 mmol) and the mixture was heated to reflux for 6 h. The mixture was cooled and brought to pH 2 with 5% aqueous HCl. The mixture was heated to reflux for 1 h. The solvents were removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The title compound, as a 1:1 mixture of diastereomers, was obtained as a lyophilized powder.

anal: ($C_{27}H_{39}N_3O_5S$)			
calc.	C, 54.37;	H, 6.53;	N, 6.56
found	C. 54.26;	H, 6.41;	N, 6.59

1.0 TFA, 0.5 H_2O
TLC: R_f 0.39 (92:8:0.1 $CXCl_3$:MeOH:HOAc)
HPLC (method A): retention time 9.62 min
FAB MS: m/z 518 (M^+ + H)
^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (m, 4H), 7.13 (m, 4H), 6.52 (d, 1H), 6.40 (d, 1H), 5.45 (m, 1H), 5.40 (m, 1H), 4.67 (m, 2H), 2.40 (s, 6H), 20.5 (s, 3H), 2.04 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H), 0.88 (s, 3H), 0.79 (s, 3H)

EXAMPLE 30

1-((7,7-DIMETHYL-2-OXO-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



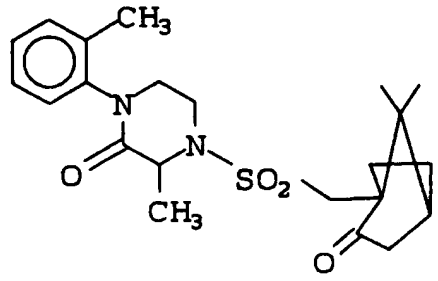
To a stirred solution of 1-t-butyloxycarbonyl-4-(2-methylphenyl)-3-piperazinone (0.25 g; 0.86 mmol) in dichloromethane (3 mL) was added TFA (1 mL). After 1 hour the solvents were removed under reduced pressure and the residue was taken up into chloroform and evaporated several times to remove excess TFA. The residue was dissolved in chloroform (5 mL) and added to the stirred solution was 10-camphorsulfonyl chloride (376 mg; 1.50 mmol) and triethylamine (0.38 mL; 2.7 mmol). After 12 hours, the mixture was diluted with chloroform (25 mL) and extracted with 5% aqueous HCl (25 mL), water (25 mL), and aqueous $NaHCO_3$ (25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 2:1 hexane-ethyl acetate as eluant. The title compound was obtained as a white foam from ether-hexane.

Anal: ($C_{21}H_{28}N_2O_4S$)			
Calc.	C, 62.35;	H, 6.98;	N, 6.93
Found	C, 61.78;	H, 6.98;	N, 6.82

TLC: R_f 0.30 (1:1 hexane-ethyl acetate)
HPLC (method A): retention time 8.15 min
FAB MS: m/z 405 (M^+ + H)

EXAMPLE 31

1-((7,7-DIMETHYL-2-OXO-BICYCLO(2.2.1) HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)-2-METHYL-3-PIPERAZINONE



To a stirred, 78°C solution of LDA (2.0 mmol) in THF (15 mL) was added a -78°C solution of 1-t-butyloxycarbonyl-4-(2-methylphenyl)-3-piperazinon (0.50 g; 1.7 mmol) in THF (5 mL). The resulting solution was stirr d for 1 hour, when iodomethan (0.125 mL; 2.0 mmol) was added. Th reaction mixture was stirred at -78°C for 30 minutes, and th n the cooling bath was remov d and th mixtur was stirr d at ambient temperature for 3 hours. Water (10 mL) and ethyl acetate (50 mL) were added. The organic layer

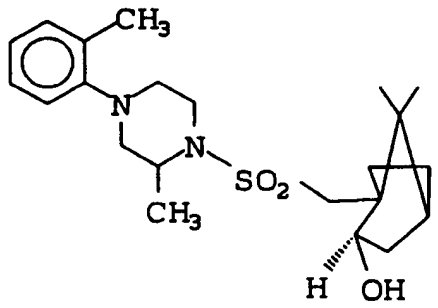
was separated and washed with wat r (25 mL) and brine (25 mL). Th organic phase was dried ($MgSO_4$), filt red, and the solvent was remov d und r r duc d pressure. The residue was purifi d by pr ssuriz d silica gel column chromatography using 85:15 hexane-ethyl acetate as eluant. The methylated product had an Rf = 0.47 (70:30 hexane-ethyl acetate) and an HPLC retention time of 8.32 min (Method A). The product (0.40 g; 1.3 mmol) was dissolved in chloroform (3 mL) and TFA (1 mL) was added. After 2 hours, the mixture was diluted with chloroform (50 mL) and extracted with aqueous $NaHCO_3$ (3 x 25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give an oil (HPLC retention time 2.95 min, Method A). The residue was dissolved in chloroform (20 mL) and to the stirred solution was added 10-camphorsulfonyl chloride (0.41 g; 1.6 mmol) and triethylamine (0.28 mL; 2.0 mmol). After 12 hours, the mixture was diluted with chloroform (25 mL) and extracted with 5% aqueous HCl (25 mL), water (25 mL), and aqueous $NaHCO_3$ (2 x 25 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 2:1 hexane-ethyl acetate as eluant. The title compound, as a 1:1 mixture of diastereomers, was obtained as a white solid from hexane-ether.

Anal: ($C_{22}H_{30}N_2O_4S$)			
Calc.	C, 63.13;	H, 7.23;	N, 6.69
Found	C, 63.46;	H, 7.09;	N, 6.74

TLC: R_f 0.27 (60:40 hexane-ethyl acetate)
HPLC (method A): retention time 8.52 min
FAB MS: m/z 419 (M^+ + H)
^1H NMR (300 MHz, $CDCl_3$): δ 7.1-7.3 (m, 8H), 4.62 (overlapping quartets, 2H), 2.21 (s, 3H), 2.20 (s, 3H), 1.68 (overlapping doublets, 6H), 1.13 (s, 3H), 1.11 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H)

EXAMPLE 32

1-((7,7-DIMETHYL-2-EXO-HYDROXY-BICYCLO (2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYL-PHENYL)-2-METHYL-PIPERAZINE



To a stirred, 0°C solution of 1-((7,7-dimethyl-2-oxo-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methyl-phenyl)-2-methyl-3-piperazinone (0.15 g; 0.36 mmol) in THF (5 mL) was added a 1.0 M solution of LAH in THF (1.1 mL; 1.1 mmol). The resulting solution was warmed to ambient temperature and stirred for 3 hours. The reaction was quenched by adding aqueous NaOH to give a white precipitate. The mixture was diluted with ethyl acetate and the solids were removed by filtration through Celite. The filtrate solvents were removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using 9:1 hexaneethyl acetate as eluant to give 1-((7,7-dimethyl-2-exo-hydroxy-bicyclo(2.2.1)heptan-1-yl)m than sulfonyl) -4-(2-m thylphenyl)-2-methyl-2,3-dehydro-piperazine (FAB MS: m/z 405 (M^+ + H); olefinic proton at 5.8 ppm in the ^1H NMR spectrum). This product (75 mg; 0.19 mmol) was dissolved in triethylsilane (2 mL) and to the stirred solution was added TFA (0.030 mL; 0.38 mmol). After 18 hours, the solvents were removed und r reduc d pressure and th residue was dissolved in thyl acetat (20 mL) and washed with aqueous $NaHCO_3$ (2 x 10 mL). Th organic phase was dri d ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pr parative revers phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The title compound, as a 1:1 mixture of diastereomers,

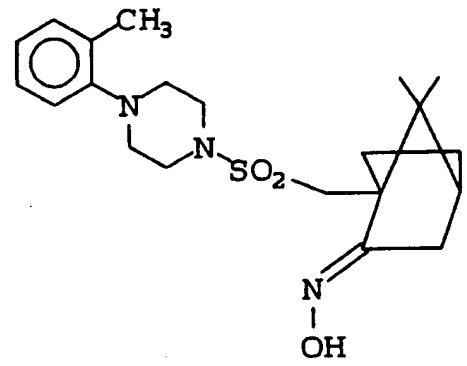
was obtained as a lyophilized powder.

Anal: ($C_{22}H_{34}N_2O_3S$)			
Calc.	C, 63.13;	H, 7.23;	N, 6.69
Found	C, 63.46;	H, 7.09;	N, 6.74

TLC: R_f 0.27 (60:40 hexane-ethyl acetate)
HPLC (method A): retention time 14.33 min
FAB MS: m/z 407 (M^+ + H)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 4H), 7.06 (m, 4H), 4.20 (m, 2H), 2.36 (s, 6H), 1.55 (overlapping doublets, 6H), 1.09 (s, 6H), 0.86 (s, 6H)

EXAMPLE 33

1-((7,7-DIMETHYL-2-OXIMINO-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



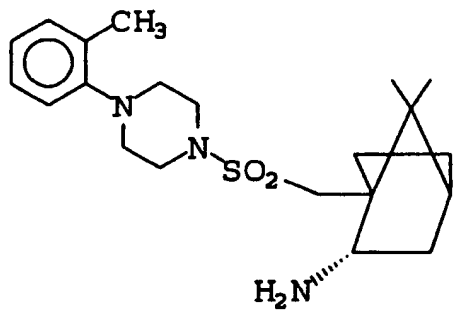
To a stirred solution of 1-((7,7-dimethyl-2-oxo-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (65.0 g; 166 mmol) in pyridine (250 mL) was added hydroxylamine hydrochloride (35.0 g; 0.504 mol). The solution was heated to 70°C for 18 h. The solvent was removed under reduced pressure, the residue was taken up in chloroform (500 mL) and washed with aqueous NaHCO3 (2 x 200 mL), water (100 mL), and 5% aqueous HCl (2 x 200 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The title compound crystallized from ethyl acetate, giving off-white needles (57 g; 84%), mp 174-175°C.

Anal: ($C_{21}H_{31}N_3O_3S$)			
Calc.	C, 62.19;	H, 7.71;	N, 10.36
Found	C, 62.29;	H, 7.63;	N, 10.15

TLC: R_f 0.40 (75:25 hexane-ethyl acetate)
HPLC (method A): retention time 9.98 min
FAB MS: m/z 406 (M^+ + H)
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (br s, 1H), 7.18 (m, 2H), 7.02 (m, 2H), 3.47 (m, 4H), 4.43 (d, J = 14.4 Hz, 1H), 3.00 (m, 4H), 2.92 (d, J = 14.4 Hz, 1H), 2.4-2.6 (m, 2H), 2.31 (s, 3H), 2.09 (d, J = 16.9 Hz, 1H), 1.95 (m, 2H), 1.80 (m, 1H), 1.32 (m, 1H), 1.08 (s, 3H), 0.87 (s, 3H)

EXAMPLE 34

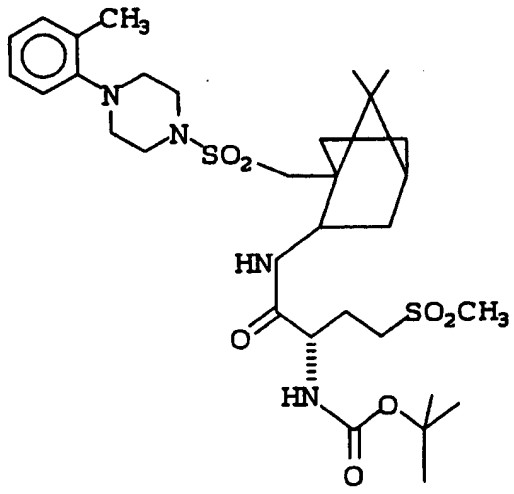
1-((7,7-DIMETHYL-2-ENDO-AMINO-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



To a stirred solution of 1-((7,7-dimethyl-2-oximino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (35.0 g; 86 mmol) in 2-methoxyethanol (500 mL) containing Raney Nickel alloy (105 0 g) was added sodium hydroxide solution (17.2 g; 430 mmol dissolved in 75 mL) dropwise over 30 min. During the addition heat and gas was evolved. The mixture was stirred at ambient temperature for16 h, at which time TLC indicated complete consumption of starting oxime and a ca. 4:1 mixture of endo (lower Rf and exo (higher Rf) amine products. The mixture was filtered through Celite and the filter-cake was washed with methanol and ethyl acetate. The solvents were removed under reduced pressure and the resulting solid was dispersed in water and filtered. The dried solid was purified by pressurized silica gel column chromatography, using a 93:3 to 94:6 A:B gradient elution (A = chloroform, B = 5% NH_4OH/MeOH). The title compound was obtained as a white foam (24 g; 70%).
FAB MS: m/z 392 (M^+ + H)

EXAMPLE 35

1-((7,7-DIMETHYL-2-ENDO-(2S-(TERT-BUTYLOXYCARBONYLAMINO)-4-(METHYLSULFONYL)-BUTYRAMIDO)-BICYCLO(2.2.1)-HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



To a stirred solution of 1-((7,7-dimethyl-2-endo-amino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazin (2.0 g; 5.1 mmol) in DMF (20 mL) was add d Na-Boc-L-m thionin sulfon (1.5 g;

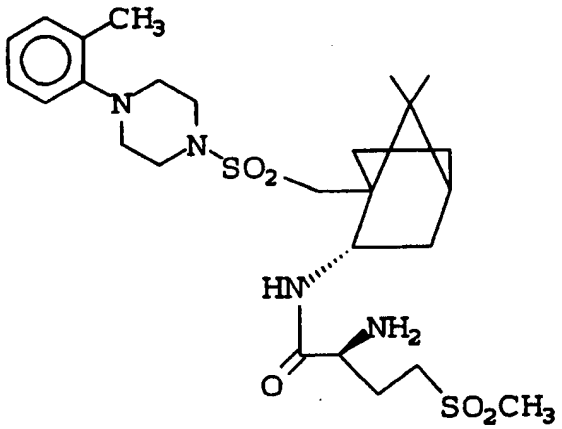
5.3 mmol), BOP reagent (2.5 g; 5.6 mmol), followed by DIEA (1.85 mL; 10.6 mmol). After being stirred at ambin t temp ratur for 1 h, more DIEA (ca. 0.1 mL) was added to obtain a pH 8 solution. Th solution was stirred for another 1 h, when the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (150 mL) and washed with 5% aqueous HCL (2 x 50 mL), water (2 x 50 mL), and aqueous NaHCO3 (2 x 75 mL). The organic phase was dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography, using 4:1 EtOAc-hexanes as eluant. The title compound was obtained as a solid from methanol (2.8 g; 85%).

Anal: ($C_{31}H_{50}N_4O_7S_2$)				
Calc.	C, 55.78;	H, 7.76;	N, 8.39	0.7 H_2O
Found	C, 55.57;	H, 7.70;	N, 8.36	

TLC: R_f 0.73 (95:5 $CHCl_3$:MeOH)
HPLC (method A): retention time 11.02 min
FAB MS: m/z 655 (M^+ + H)
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (m, 2H), 7.04 (m, 2H), 5.38 (br d, 1H), 4.32 (q, J = 7.4 Hz, 1H), 4.22 (m, 1H), 2.94 (s, 3H), 2.32 (s, 3H), 1.45 (s, 9H), 1.00 (s, 3H), 0.98 (s, 3H)

EXAMPLE 36

1-((7,7-DIMETHYL-2-ENDO-(2S-AMINO-4-(METHYLSULFONYL)-BUTYRAMIDO)-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



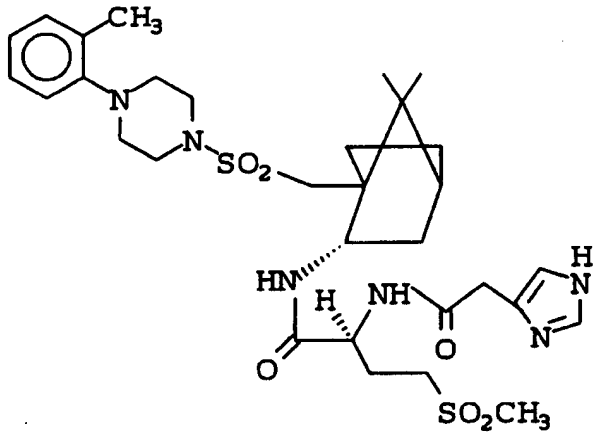
To a stirred solution of 1-((7,7-dimethyl-2-endo-(2S-tert-butyloxycarbonylamino-4-(methylsulfonyl) butyramido)-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl) -4-(2-methylphenyl)piperazine (2.5 g; 3.8 mmol) in dichloromethane (15 mL) was added TFA (5 mL). After 1 h, the solvents were removed under reduced pressure. The residue was dissolved in chloroform (100 mL) and washed with aqueous NaHCO3 (2 x 75 mL). The organic phase was dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 95:5:0.5 CHCl3:MeOH:NH4OH as eluant. The title compound was obtained as a white foam from EtOAc (1.9 g; 90%).

Anal: ($C_{26}H_{42}N_4O_5S_2$)				
Calc.	C, 56.14;	H, 7.75;	N, 9.29	0.55 EtOAc
Found	C, 55.94;	H, 7.74;	N, 9.31	

TLC: R_f 0.17 (95:5:0.5 $CHCl_3$:MeOH:NH4OH)
HPLC (m thod A): r t ntion time 8.50 min
FAB MS: m/z 455 (M^+ + H)
^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 8.4 Hz, 1H), 7.20 (m, 2H), 7.02 (m,2H), 4.43 (m, 1H), 2.94 (s, 3H), 2.31 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H)

EXAMPLE 37

1-((7,7-DIMETHYL-2-ENDO-(2S-(IMIDAZOL-4-YLACETYLAMINO)-4-(METHYLSULFONYL)BUTYRAMIDO)-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



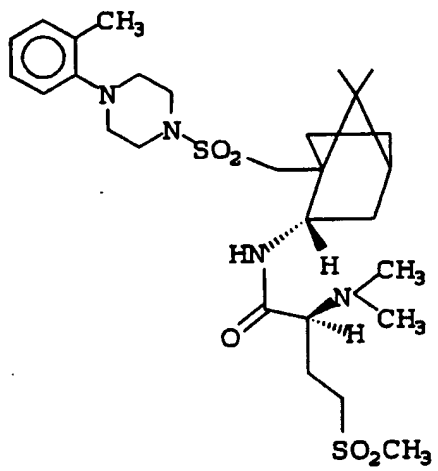
To a stirred solution of 1-((7,7-dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)butyramido)-bicyclo(2.2.1)-heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl) piperazine (250 mg; 0.45 mmol) in DMF (5 mL) was added 4-imidazole acetic acid hydrochloride (110 mg; 0.68 mmol), BOP (265 mg; 0.60 mmol), and DIEA (0.355 mL; 2.0 mmol). The solution was stirrred at ambient temperature for 18 h. The solvent was removed under reduced pressure, and the residue was suspended in EtOAc (100 mL) and filtered through Celite to remove red polymer. The filtrate was washed with 5% aqueous HCl (50 mL), water (50 mL), and aqueous NaHCO3 (2 x 50 mL). The organic phase was dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 92:8:0.8 CHCl3:MeOH:NH4OH as eluant. The title compound was obtained as a solid from EtOAc (230 mg; 78%).

Anal: ($C_{31}H_{46}N_6O_6S_2$)					
Calc.	C, 53.74;	H, 7.32;	N, 11.26	0.6 EtOAc,	$1.7H_2O$
Found	C, 53.74;	H, 7.00;	N, 11.25		

TLC: R_f 0.22 (90:10:0.5 $CHCl_3$:MeOH:NH4OH)
HPLC (method A): retention time 8.49 min
FAB MS: m/z 663 (M^+ + H)
^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (overlapping singlet and broad singlet, 2H), 7.38 (br d, 1H), 7.18 (m, 2H), 7.02 (m, 2H), 6.96 (s, 1H), 4.68 (br q, J = ca. 5 Hz, 1H), 4.27 (m, 1H) 3.62 (br s, 2H), 2.92 (s, 3H), 2.30 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H)

EXAMPLE 38

1-((7,7-DIMETHYL-2-ENDO-(2S-(DIMETHYLAMINO)-4-(METHYLSULFONYL)BUTYRAMIDO)-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



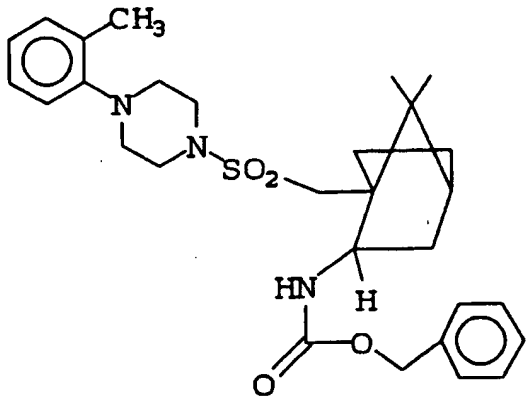
To a stirred solution of 1-((7,7-dimethyl-2-endo-(2S-amino-4-(methylsulfonyl)butyramido)-bicyclo(2.2.1)-heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl) piperazine (250 mg; 0.45 mmol) in 1:1 HOAc:MeOH (10 mL) was added 37% aqueous formaldehyde (2 mL) and NaBH3CN (60 mg; 0.95 mmol). The solution was stirrred at ambient temperature for 4 h. Aqueous NaHCO3 (2 mL) was added and the solvents were removed under reduced pressure. The residue was suspended in EtOAc (75 mL) and washed with water (2 x 50 mL). The organic phase was dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The title compound was obtained as a white foam from EtOAc (190 mg; 72%).

Anal: ($C_{28}H_{46}N_4O_5S_2$)				
Calc.	C, 57.56;	H, 8.01;	N, 9.20	0.3 EtOAc,
Found	C, 57.41;	H, 7.98;	N, 9.20	

TLC: R_f 0.26 (95:5:0.5 $CHCl_3$:MeOH:NH4OH)
HPLC (method A): retention time 9.10 min
FAB MS: m/z 583 (M^+ + H)
^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (Br s, 1H), 7.18 (m, 2H), 7.02 (M, 2H), 4.37 (m, 1H), 2.92 (s, 3H), 2.36 (s, 6H), 2.30 (s, 3H), 1.02 (s, 3H), 0.98 (s, 3H)

EXAMPLE 39

1-((7,7-DIMETHYL-2-ENDO-BENZYLOXYCARBONYLAMINO-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



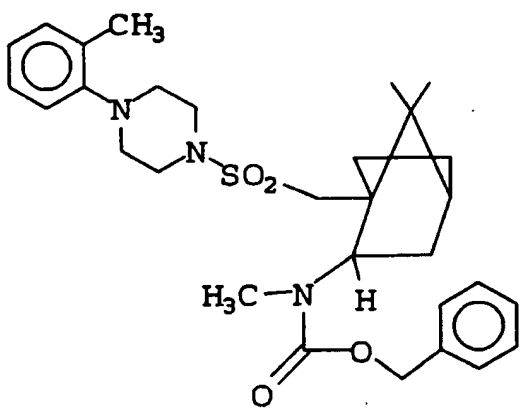
To a 0°C stirred solution of 1-((7,7-dimethyl-2-endo-amino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.20 g; 3.07 mmol) in CHCl3 (100 mL) was added DIEA (0.80 mL; 4.6 mmol) and benzyl chloroformate (0.58 g; 3.4 mmol). The solution was stirrred at 0°C for 1 h and then at ambient temperature for 4 h. The reaction mixture was washed with 5% aqueous HCl (2 x 50 mL) and aqueous NaHCO3 (100 mL). The organic phase was dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 1:4 EtOAc-hexanes as eluant. The title compound was obtained as a white foam. (1.45 g; 90%).

Anal: ($C_{29}H_{39}N_3O_4S$)					
Calc. Found	C, 65.75; C, 65.90;	H, 7.53; H, 7.49;	N, 7.77 N, 7.80	0.15 EtOAc,	0.1 H2O

TLC: R_f 0.38 (1:3 EtOAc:hexanes)
HPLC (method A): retention time 12.18 min
FAB MS: m/z 526 (M^+ + H)

EXAMPLE 40

1-((7,7-DIMETHYL-2-ENDO-METHYL(BENZYLOXYCARBONYL)AMINO-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE



To a 0°C stirred solution of 1-((7,7-dimethyl-2-endo-benzyloxycarbonylamino-bicyclo(2.2.1)heptan-1-yl)-methanesulfonyl)-4-(2-methylphenyl)piperazine (1.46 g; 2.78 mmol) in DMF (20 mL) was added iodomethane (0.435 mL; 7.00 mmol) and sodium hydride (0.139 mg of a 60% dispersion in mineral oil; 3.48 mmol). The solution was stirrred at 0°C for 1 h and then at ambient temperature for 18 h. The reaction mixture was treated with HOAc (1 mL) and the solvents were removed under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with aqueous NaHCO3 (2 x 50 mL). The organic phase was dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 1:5 EtOAc-hexanes as eluant. The title compound was obtained as a white foam. (1.40 g; 93%).

Anal: ($C_{30}H_{41}N_3O_4S$)				
Calc.	C, 66.03;	H, 7.70;	N, 7.70	0.33 H20
Found	C, 66.03;	H, 7.63;	N, 7.68	

TLC: R_f 0.44 (1:4 EtOAc:hexanes)
HPLC (method A): retention time 12.86 min
FAB MS: m/z 540 (M^+ + H)
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.45 (m, 5H), 7.20 (m, 2H), 7.02 (m, 2H), 5.11 (AB quartet, 2H), 4.83 (m, 1H), 3.03 (s, 3H), 2.32 (s, 3H), 1.04 (s, 3H), 0.96 (s, 3H)

EXAMPLE 41

1-((7,7-DIMETHYL-2-ENDO-METHYL(2S-AMINO-4-(METHYLSULFONYL)BUTANOYL)AMINO-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE

To a stirred, argon purged solution of 1-((7,7-dimethyl-2-endo-methyl(benzyloxycarbonyl)amino-bicyclo-(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.1 g; 2.0 mmol) in 96:4 MeOH-HCO2H (25 mL) was added palladium black (0.4 g). The reaction mixture was stirrred for 16 h at ambient temperature. The catalyst was removed by filtration through Celite, and the filtrate solvents were removed under reduced pressure. The r sidu was purified by pr ssuriz d silica g l column chromatography using 95:5:0.5 CHCl3:MeOH:NH4OH as eluant. The product, 1-((7,7-dimethyl-2-endo-methylamino-bicyclo(2.2.1)-heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine, was obtained as a white foam. (0.79 g; 95%). To a stirred solution of 1-((7,7-dimethyl-2- ndo-methylamino-bicyclo(2.2.1)h ptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)pip razine (0.700 g; 1.73 mmol) in CHCl3 (60 mL) was added the acid fluorid of Nα-Fmoc-L-methionine sulfone (1.23 g; 3.03 mmol) and DIEA (0.52 mL; 3.0 mmol). The mixture was stirr d at ambient temperature for 24 h, and then extracted with 5% aqueous HCl (30 mL), water (30 mL), and aqueous

NaHCO3 (2 x 30 mL). Th organic phase was dri d (MgSO4), filter d, and the solvent was r moved under r duced pressure. Th residue was dissolv d in DMF (10 mL), and to th solution was add d di thylamin (2 mL). The mixture was stirred at ambient temperature for 6 h. The solvents were removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using 95:5:0.5 CHCl3:MeOH:NH4OH as eluant. The title compound was obtained as a foam from CHCl3-ether (0.71 g; 61%).

Anal: ($C_{27}H_{44}N_4O_5S_2$)					
Calc.	C, 56.26;	H, 7.80;	N, 9.40	0.1 CHCl3,	0.2 ether
Found	C, 56.21;	H, 7.79;	N, 9.22		

TLC: R_f 0.10 (95:5:0.5 CHCl3:MeOH:NH4OH)
HPLC (method A): retention time 9.01 min
FAB MS: m/z 569 (M^+ + H)
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (m, 2H), 7.03 (m, 2H), 5.20 (ddd, 1H), 3.95 (dd, J=, 9.3, 4.1 Hz, 1H), 3.18 (s, 3H), 2.91 (s, 3H), 2.30 (s, 3H), 1.06 (s, 3H), 0.96 (s, 3H)

EXAMPLE 42

1-((7,7-DIMETHYL-2-ENDO-METHYL(2S-DIMETHYLAMINO-4-(METHYLSULFONYL)BUTANOYL)AMINO-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE

To a stirred solution of 1-((7,7-dimethyl-2-endo-methyl(2S-amino-4-(methylsulfonyl)butanoyl)amino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (150 mg; 0.264 mmol) in 1:1 HOAc:MeOH (6 mL) was added 37% aqueous formaldehyde (1 mL) and NaBH3CN (30 mg; 0.47 mmol). The solution was stirrred at ambient temperature for 4 h. Aqueous NaHCO3 (1 mL) was added and the solvents were removed under reduced pressure. The residue was suspended in EtOAc (50 mL) and washed with water (2 x 25 mL). The organic phase was dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The residue was purified by preparative reverse phase HPLC using a water-acetonitrile gradient containing 0.1% TFA. The TFA salt of the title compound was obtained as a lyophilized powder.

Anal: ($C_{29}H_{48}N_4O_5S_2$)					
Calc.	C, 44.88;	H, 5.94;	N, 6.16	2.5 TFA,	1.5 H20
Found	C, 44.80;	H, 5.94;	N, 6.18		

TLC: R_f 0.45 (95:5:0.5 $CHCl_3$:MeOH:NH4OH)
HPLC (method A): retention time 9.04 min
FAB MS: m/z 597 (M^+ + H)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.2-7.3 (m, 4H), 5.15 (m, 1H), 4.79 (br t, 1H), 3.21 (s, 3H), 2.98 (s, 3H), 2.95 (s, 6H), 2.43 (s, 3H), 1.07 (s, 3H), 0.97 (s, 3H)

EXAMPLE 43

1-((7,7-DIMETHYL-2-ENDO-(4-IMIDAZOLYL)ACETYL)AMINO-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINONE

To a stirred solution of 1-((7,7-dimethyl-2-endo-amino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.50 g; 3.84 mmol) in DMF (30 mL) was added 4-imidazole acetic acid hydrochloride (0.938 g; 5.76 mmol), BOP (2.13 g; 4.80 mmol), and DIEA (2.61 mL; 15.0 mmol). The reaction mixture was stirrr d for 24 h at ambient t mperature, and the solvent was remov d under reduced pressure. The residue was suspended in EtOAc (100 mL) and filtered through C lite to remove r d polymer. The filtrat was washed with aqueous NaHCO3 (2 x 50 mL) and water (2 x 50 mL). Th organic phase was dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatograpby using 92:8:0.8 CHCl3:MeOH:NH4OH as eluant. The title compound was obtained as white foam.

FAB MS: m/z 500 (M^+ + H)

EXAMPLE 44

1-((7,7-DIMETHYL-2-ENDO-(2-(4-IMIDAZOLYL)PROPANOYL)AMINO-BICYCLO(2.2.1)HEPTAN-1-YL)-METHANESULFONYL)-4-(2-METHYLPHENYL)-3-PIPERAZINE

To a stirred solution of 1-((7,7-dimethyl-2-endo-amino-bicyclo(2.2.1)heptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.1 g; 2.8 mmol) in DMF (25 mL) was added 2-(1-benzyloxymethyl-5-imidazolyl)-propionic acid hydrochloride (0.920 g; 3.10 mmol), BOP (1.35 g; 3.05 mmol), and DIEA (1.50 mL; 8.61 mmol). The reaction mixture was stirrred for 1 h at ambient temperature, and more DIEA (ca. 0.2 mL) was added to bring the mixture to pH 8. After another 1 h, the solvent was removed under reduced pressure. The residue was dissolved in CHCl3 (150 mL) and washed with aqueous NaHCO3 (2 x 50 mL) and water (2 x 50 mL). The organic phase was dried (MgSO4), filtered, and the solvent was removed under reduced pressure to give a solid. Recrystallization from EtOAc gave crystals (0.51 g) which, by ^{1}H NMR analysis, proved to be a 90:10 mixture of isomers (product A). The filtrate was purified by pressurized silica gel column chromatography using 95:5 CHCl3:MeOH as eluant, giving a white foam (1.0 g). ^{1}H NMR indicated this material to be a 1:2 mixture of isomers (product B). Products A and B were individually deblocked by hydrogenation for 24 h at ambient temperature in 3:1 MeOH:HOAc using 25 weight% palladium black under 1 atmosphere of hydrogen. The catalyst was removed by filtration through Celite and the solvents were removed under reduced pressure.catalyst was removed by filtration through Celite, and the filtrate solvents were removed under reduced pressure. The residue derived from product A was purified by preparative reverse phase HPLC using a water-acetonitrile gradient containing 0.1% TFA. The TFA salt of the title compound (90:10 mixture by ^{1}H NMR) was obtained as a lyophilized powder. Product B was purified by pressurized silica gel column chromatography using 95:5:0.5 CHCl3:MeOH:NH4OH as eluant. The title compound was obtained as white foam from CHCl3-ether (1:2 mixture by ^{1}H NMR). The two isomers had identical chromatographic behavior.

Anal: ($C_{27}H_{37}N_5O_3S$)					
Calc.	C, 60.36;	H, 7.49;	N, 12.46	0.25 $CHCl_3$,	0.25 ether
Found	C, 60.49;	H, 7.26;	N, 12.48		

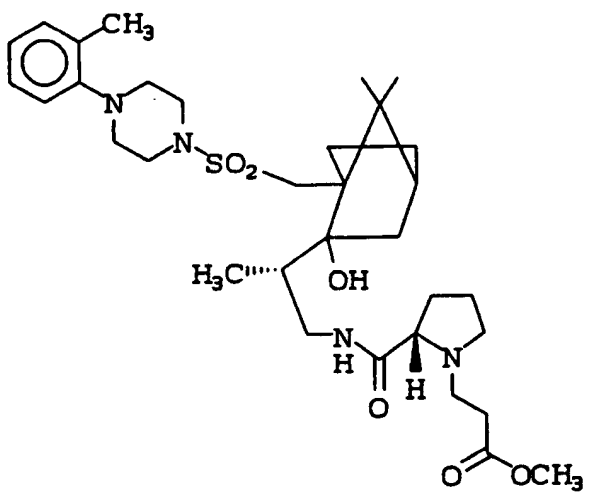
TLC: R_f 0.30 (93:7:0.7 CHCl3:MeOH:NH4OH)
HPLC (method A): retention time 8.79 min
FAB MS: m/z 514 (M^+ + H)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (br s, 1H), 7.20 (m, 2H), 7.0 (m, 3H), 4.40 (m, 1H), 2.30, 2.29 (two singlets, ca. 2:1 ratio, 3H), 1.57, 1.53 (two doublets, J = 7 Hz, ca. 2:1 ratio, 3H), 1.00 (s, 3H), 0.96 (s, 3H)
L-369,076

Anal: ($C_{27}H_{37}N_5O_3S$)				
Calc.	C, 48.91;	H, 5.36;	N, 9.03	2.3 TFA
Found	C, 48.99;	H, 5.21;	N, 9.03	

TLC: R_f 0.30 (93:7:0.7 CHCl3:MeOH:NH4OH)
HPLC (method A): retention time 8.79 min
FAB MS: m/z 514 (M^+ + H)
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.70 (d, 1H), 7.25 (m, 2H), 7.20 (s, 1H), 7.15 (m, 2H), 4,40 (m, 1H), 4.03 (q, J = 7Hhz, 1H), 2.38 (s, 3H), 1.57 (d, J = 7Hz, 3H), 1.00 (s, 3H), 0.95 (s, 3H)

EXAMPLE 45

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(L-N-(METHOXYCARBONYLETHYL)PROLYL)AMINO)-PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



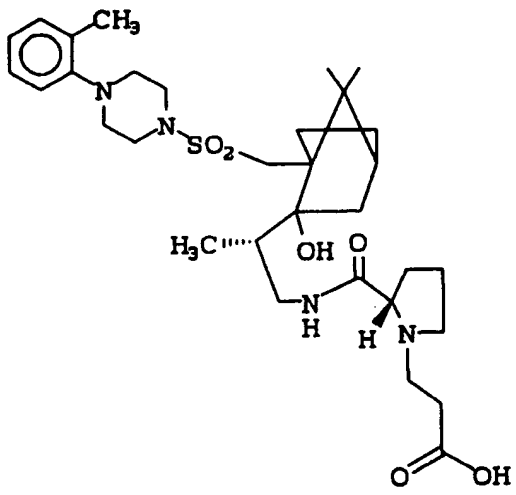
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(L-prolyl)amino)propyl(2.2.1)-bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.50 g; 2.74 mmol) in methanol (15 mL) was added methyl acrylate (0.310 mL; 3.43 mmol). After 72 h at ambient temperature, the solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: ($C_{33}H_{52}N_4O_6S$)				
Calc.	C, 53.10;	H, 6.59;	N, 6.82	1.65 TFA
Found	C, 53.09;	H, 6.58;	N, 6.88	

TLC: R_f 0.55 (95:5 CHCl3:MeOH)
HPLC (method A): retention time 9.45 min
FAB MS: m/z 633 (M^+ + H)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (m, 2H), 7.03 (m, 2H), 4.55 (m, 1H), 3.72 (s, 3H), 2.32 (s, 3H), 1.15 (s, 3H), 1.04 (s, 3H), 1.01 (d, J = 6 Hz, 3H)

EXAMPLE 46

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(L-N-(CARBOXYETHYL)PROLYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



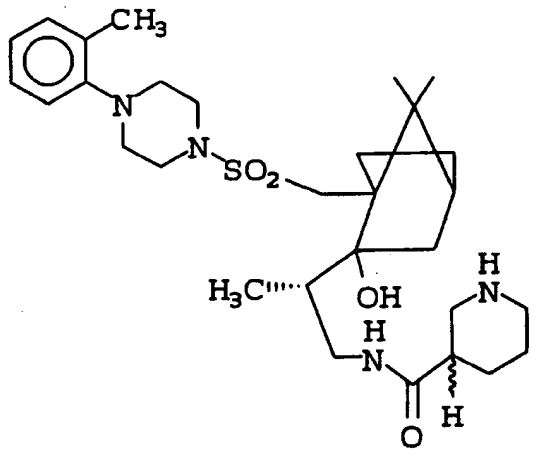
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(L-N-(methoxycarbonylethyl)prolyl)-amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.00 g; FW = 821; 1.22 mmol) in THF (15 mL) was added 1 M NaOH until a pH 10 solution persisted for 1 h. The solution was evaporated under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: ($C_{32}H_{50}N_4O_6S$)				
Calc.	C, 51.88;	H, 6.34;	N, 6.80	1.8 TFA
Found	C, 51.87;	H, 6.28;	N, 6.82	

TLC: R_f 0.40 (80:20:2 CHCl3:MeOH:NH4OH)
HPLC (method A): retention time 8.88 min
FAB MS: m/z 619 (M^+ + H)
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (br s 1H), 7.20 (m, 2H), 7.05 (m, 2H), 2.33 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H), 0.99 (d, J = 6 Hz, 3H)

EXAMPLE 47

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(3-PIPERIDINYLCARBONYL)AMINO)PROPYL-BICYCLO-(2.2.1)HEPTAN-1-YL) METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



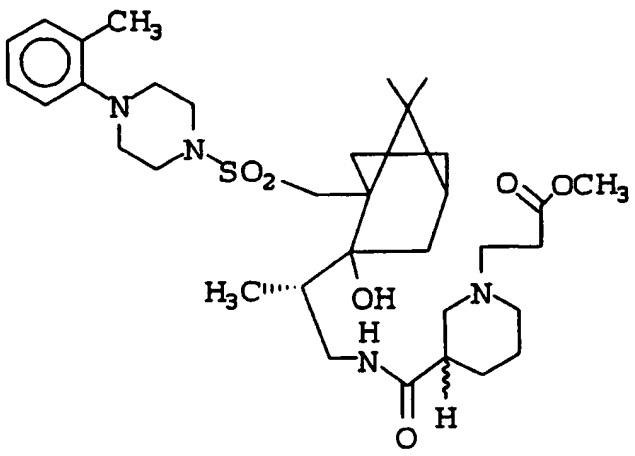
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (2.50 g; 5.57 mmol) in DMF (35 mL) was added N-Fmoc-piperidine-3-carboxylic acid (2.15 g; 6.13 mmol), BOP (2.75 g; 6.20 mmol), and DIEA (2.16 mL; 12.4 mmol). After 16 h, diethylamine (6 mL) was added and the solution was stirred at ambient temperature for 4 h. The solvents were removed under reduced pressure and the residue was dissolved in EtOAc (150 mL) and washed with aquous NaHCO3 (2 x 75 mL) and water (2 x 75 mL). The organic phase was dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography, using 93:7:0.7 CHCl3:MeOH:NH4OH as eluant. The title compound (1:1 mixture of diastereomers) was obtained as a white foam.

Anal: ($C_{30}H_{48}N_4O_4S$)				
Calc.	C, 56.37;	H, 7.49;	N, 8.54	0.8 $CHCl_3$
Found	C, 56.49;	H, 7.44;	N, 8.50	

TLC: R_f 0.40 (90:10:1 $CHCl_3$:MeOH:NH_4OH)
HPLC (method A): retention time 8.67 min
FAB MS: m/z 561 (M^+ + H)
^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (br s, 1H), 7.20 (m, 2H), 7.02 (m, 2H), 2.30 (s, 3H), 1.17 (s, 3H), 1.00-1.04 (overlapping singlet and doublet, 6H)

EXAMPLE 48

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(3-(1-METHOXYCARBONYLETHYL)-PIPERIDINYLCARBONLY)AMINO)PROPLY-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



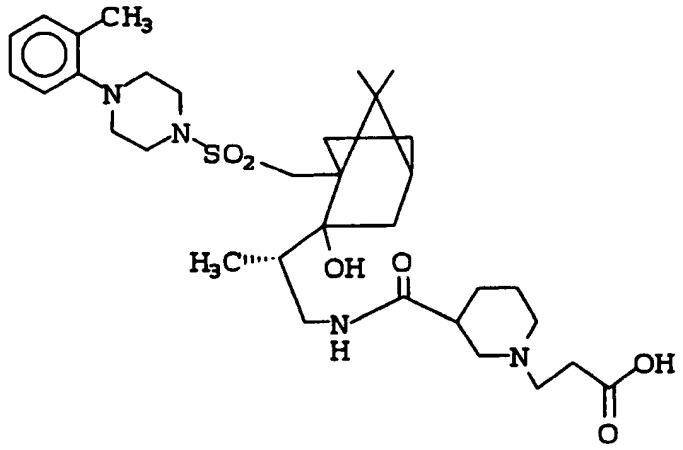
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(3-piperidinylcarbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.50 g; 0.89 mmol) in methanol (10 mL) was added methyl acrylate (0.120 mL; 1.34 mmol). After 72 h at ambient temperature, the solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound (1:1 mixture of diastereomers) was obtained as a lyophilized powder.

Anal: ($C_{34}H_{54}N_4O_6S$)					
Calc.	C, 55.40;	H, 7.06;	N, 7.08	1.25 TFA,	0.1 H20
Found	C, 55.39;	H, 7.05;	N, 7.03		

TLC: R_f 0.35 (95:5 CHCl3:MeOH)
HPLC (method A): retention time 10.71 min
FAB MS: m/z 647 (M^+ + H)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 2H), 7.02 (m, 2H), 3,72, 3,69 (two singlets, 3H), 2.32, 2.31 (two singlets, 3H), 1.16, 1.15 (two singlets, 3H), 0.98-1.04 (two coincident singlets and two overlapping doublets, 6H)

EXAMPLE 49

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(3-(1-CARBOXYETHYL)PIPERIDINYLCARBONYL)-AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL) PIPERAZINE



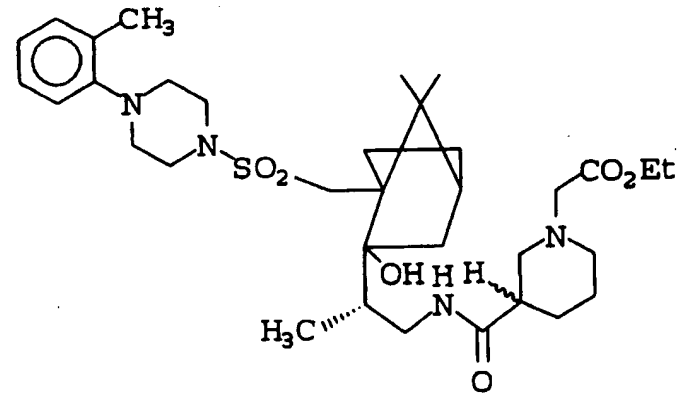
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(3-(1-methoxycarbonyl)-piperidinylcarbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.30 g; 0.46 mmol) in THF (10 mL) was added 1 M NaOH until a pH 10 solution persisted for 1 h. The solution was evaporated under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound (1:1 mixture of diastereomers) was obtained as a lyophilized powder.

Anal: ($C_{33}H_{52}N_4O_6S$)					
Calc.	C, 51.59;	H, 6.44;	N, 6.54	1.9 TFA,	0.4 H20
Found	C, 51.60;	H, 6.44;	N, 6.83		

TLC: R_f 0.15 (80:20:2 CHCl3:MeOH:NH4OH)
HPLC (method A): retention time 10.27 min
FAB MS: m/z 633 (M^* + H)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 2H), 7.05 (m, 2H), 2.39, 2.32 (two singlets, 3H), 1.12, 1.11 (two singlets, 3H), 0.95-1.03 (two coincident singlets and two overlapping doublets, 6H)

EXAMPLE 50

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(3-(1-ETHOXYCARBONYLMETHYL)-PIPERIDINYLCARBONYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



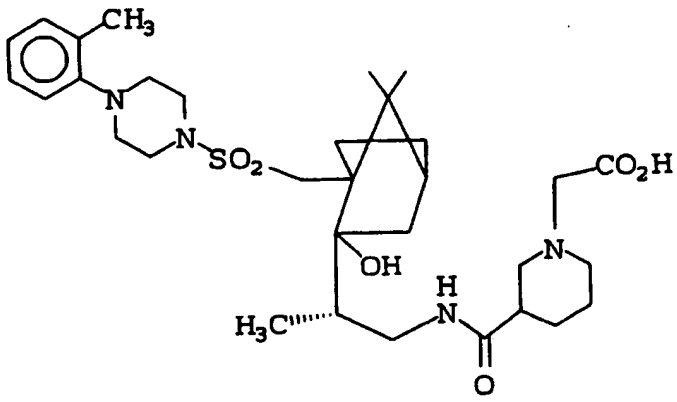
To a stirred solution of 1-((7,7-dimethyl-2- xo-hydroxy-2-endo-2-(1-(3-piperidinylcarbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)m thanesulfonyl)-4-(2-m thylphenyl)piperazin (0.50 g; 0.89 mmol) in DMF (5 mL) was added ethyl bromoacetate (0.110 mL; 0.99 mmol) and DIEA (0.172 mL; 0.99 mmol). After 24 h at ambient temperature, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc (50 mL) and washed with 5% aqueous citric acid (25 mL), water (25 mL), and aqueous NaHCO3 (25 mL). The organic phase was dried (MgSO4), filtered, and the solvents were removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography, using 1:1 EtOAc:CHCl3 as eluant. The title compound (1:1 mixture of diastereomers) was obtained as a white foam.

Anal: ($C_{34}H_{54}N_4O_6S$)				
Calc.	C, 58.66;	H, 7.77;	N, 7.93	0.5 $CHCl_3$
Found	C, 58.87;	H, 7.83;	N, 7.88	

TLC: R_f 0.28 (1:1 $CHCl_3$:EtOAc)
HPLC (method A): retention time 9.76 min
FAB MS: m/z 647 (M^+ + H)
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.2 (very br s, 1H), 7.18 (m, 2H), 7.03 (m, 2H), 4.20 (two very closely spaced quartets, 2H), 2.30, 2.31 (two singlets, 3H), 1.28 (t, J = 7 Hz, 3H), 1.07, 1.08 (two singlets, 3H), 1.03-1.08 (two coincident singlets and two overlapping doublets, 6H)

EXAMPLE 51

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(3-(1-CARBOXYMETHYL)PIPERIDINYLCARBONYL)-AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(3-(1-methoxycarbonyl)-piperidinylcarbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.360 g; 0.555 mmol) in THF (5 mL) was added 1 M NaOH until a pH 10 solution persisted for 1 h. The solution was made acidic by the addition of HOAc (1 mL) and evaporated under reduced pressure. The residue was suspended in CH2Cl2 and filtered. The filtrate was evaporated under reduced pressure several times from CH2Cl2 to give the title compound (1:1 mixture of diastereomers) as a white foam.

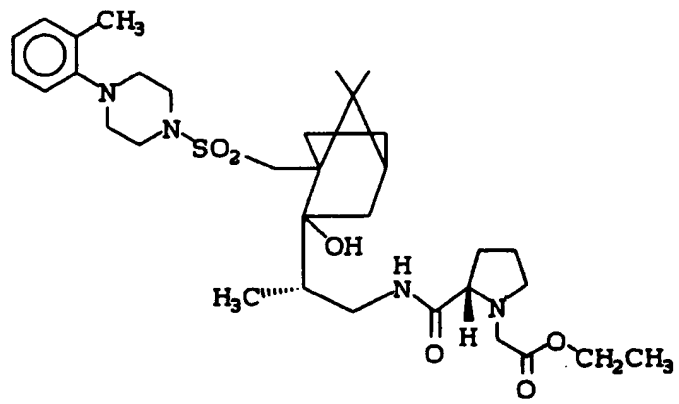
Anal: ($C_{32}H_{50}N_4O_6S$)				
Calc.	C, 58.27;	H, 7.62;	N, 7.99	1.0 NaOAc
Found	C, 58.47;	H, 7.71;	N, 7.90	

TLC: R_f 0.55 (85:15 CHCl3:MeOH)
HPLC (m thod A): retention time 8.77 min

FAB MS: m/z 619 (M^+ + H)
^{1}H NMR (300 MHz, CD_3OD): δ 7.15 (m, 2H), 7.05 (d, J=7.3 Hz, 1H), 6.96 (t, J=7.3 Hz, 1H), 2.31 (s, 3H), 1.17 (s, 3H), 1.03 (s, 3H), 0.98 (d, J=6 Hz, 3H)

EXAMPLE 52

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(L-N-(ETHOXYCARBOXYMETHYL)PROLYL)AMINO)-PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL) PIPERAZINE



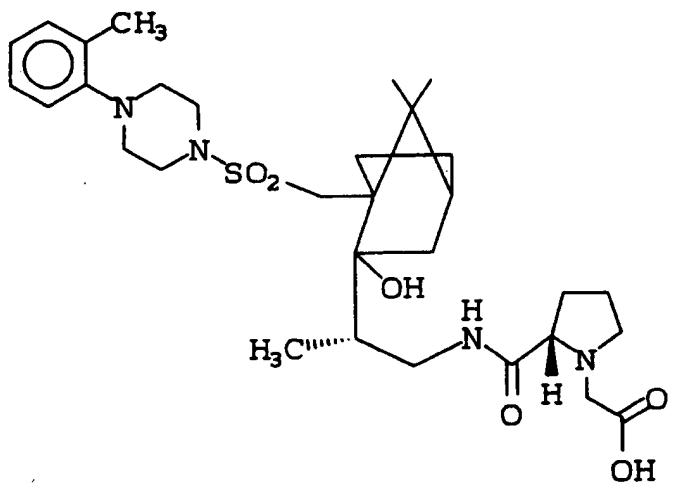
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(L-prolyl)amino)propyl(2.2.1)-bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.20 g; 0.37 mmol) in DMF (5 mL) was added ethyl bromoacetate (0.045 mL; 0.40 mmol) and DIEA (0.071 mL; 0.41 mmol). After 24 h at ambient temperature, the solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: ($C_{33}H_{52}N_4O_6S$)				
Calc.	C, 54.25;	H, 6.79;	N, 7.07	1.4 TFA
Found	C, 54.25;	H, 6.78;	N, 7.02	

TLC: R_f 0.50 (1:1 EtOAc:CHCl3)
HPLC (method A): retention time 9.68 min
FAB MS: m/z 633 (M^+ + H)
^{1}H NMR (400 MHz, CD_3OD): δ 7.17 (m, 2H), 7.06 (d, J=6Hz, 1H), 6.98 (t, J=6Hz, 1H), 4.25 (m, 3H), 4.08 (d, J=15 Hz, 1H), 2.32 (s, 3H), 1.27 (t, J=7 Hz, 3H), 1.18 (s, 3H), 1.03 (s, 3H), 1.01 (d, J=6 Hz, 3H)

EXAMPLE 53

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(L-N-(CARBOXYMETHYL)PROLYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



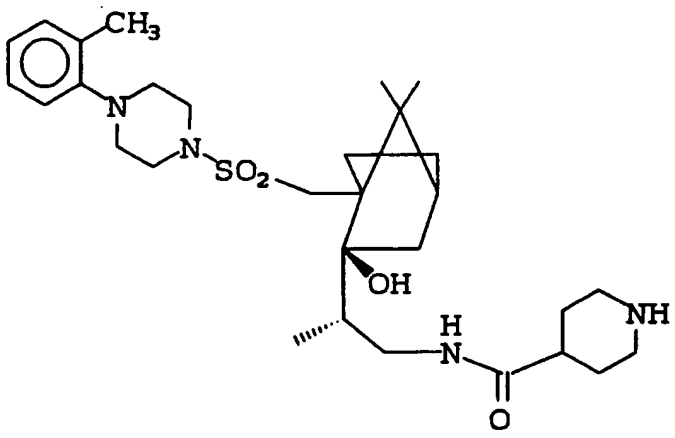
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(L-(N-ethoxycarbonylmethyl)prolyl)-amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.20 g; 0.32 mmol) in THF (5 mL) was added 1 M NaOH until a pH 10 solution persisted for 1 h. The solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: ($C_{31}H_{48}N_4O_6S$)				
Calc.	C, 52.64;	H, 6.43;	N, 7.22	1.5 TFA
Found	C, 52.49;	H, 6.51;	N, 7.22	

TLC: R_f 0.40 (80:20:2 CHCl3:MeOH:NH4OH)
HPLC (method A): retention time 8.79 min
FAB MS: m/z 605 (M^+ + H)
^{1}H NMR (400 MHz, CD_3OD): δ 7.17 (m, 2H), 7.07 (d J = 5 Hz, 1H), 6.99 (t, J = 5 Hz, 1H), 4.30 (dd, J = 4, 5 Hz, 1H), 4.21 (d, J = 14 Hz, 1H), 4.04 (d, J = 14 Hz, 1H), 2.32 (s, 3H), 1.18 (s, 3H), 1.03 (s, 3H), 1.01 (d, J = 7 Hz, 3H)

EXAMPLE 54

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(4-PIPERIDINYLCARBONYL)AMINO)PROPYL-BICYCLO-(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



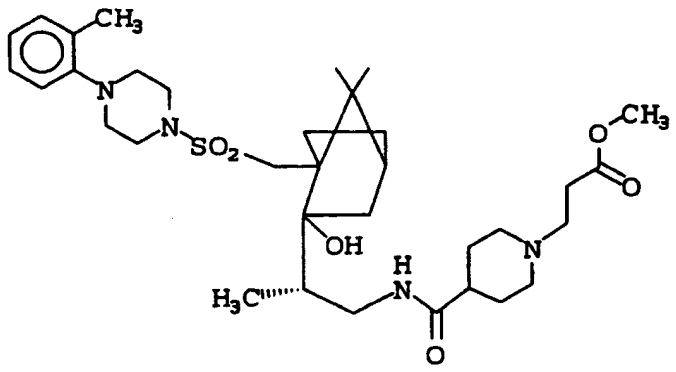
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (1.50 g; 3.34 mmol) in DMF (20 mL) was added N-Fmoc-piperidine-4-carboxylic acid (1.29 g; 3.67 mmol), BOP (1.64 g; 3.70 mmol), and DIEA (1.28 mL; 7.34 mmol). After 16 h, diethylamine (5 mL) was added and the solution was stirred at ambient temperature for 4 h. The solvents were removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: ($C_{30}H_{48}N_4O_4S$)					
Calc.	C, 51.93;	H, 6.43;	N, 7.15	1.95 TFA,	0.05 H20
Found	C, 51.93;	H, 6.36;	N, 7.28		

TLC: R_f 0.15 (90:10:1 CHCl3:MeOH:NH4OH)
HPLC (method A): retention time 8.33 min
FAB MS: m/z 561 (M^+ + H)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 3H), 7.08 (m, 2H), 2.33 (s, 3H), 1.14 (s, 3H), 1.02 (s, 3H), 1.00 (d, J = 6 Hz, 3H)

EXAMPLE 55

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(4-(1-METHOXYCARBONYLETHYL)-PIPERIDINYLCARBONYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



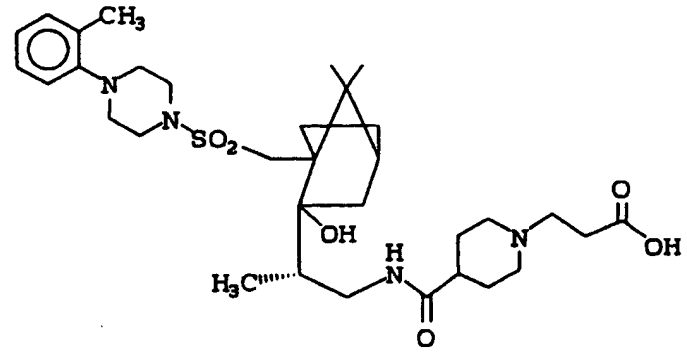
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(4-piperidinylcarbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.30 g; 0.53 mmol) in methanol (5 mL) was added methyl acrylate (0.072 mL; 0.80 mmol). After 48 h at ambient temperature, the solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: ($C_{34}H_{54}N_4O_6S$)					
Calc.	C, 53.04;	H, 6.65;	N, 6.60	1.75 TFA,	0.15 H2O
Found	C, 53.05;	H, 6.62;	N, 6.69		

TLC: R_f 0.25 (95:5 CHCl3:MeOH)
HPLC (method A): retention time 9.02 min
FAB MS: m/z 647 (M^+ + H)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (br t, 1H), 7.21 (m, 2H), 7.09 (m, 2H), 3.72 (s, 3H), 2.33 (s, 3H), 1.15 (s, 3H), 1.00-1.02 (overlapping s and d, 6H)

EXAMPLE 56

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(4-(1-CARBOXYETHYL)PIPERIDINYLCARBONYL)-AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL) PIPERAZINE



To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2- ndo-2-(1-(3-(1-m thoxycarbonyl)-piperidinylcarbonyl)amino)propyl-(2.2.1)bicycloh ptan-1-yl) m than sulfonyl)-4-(2-methylphenyl)piperazine (0.15 g; 0.23 mmol) in THF (5 mL) was added 1 M NaOH until a pH 10 solution persisted for 1 h. The

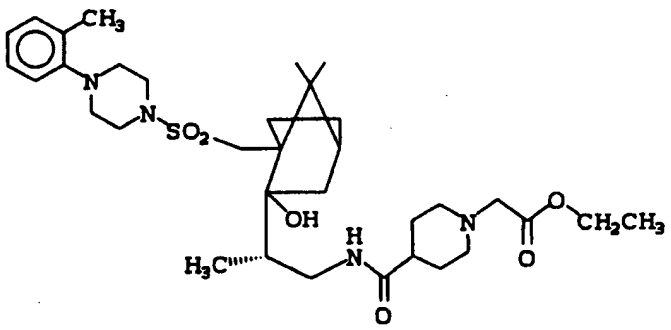
solution was evaporated under r duced pressur and the r sidu was purifi d by preparative reverse phase HPLC using an acetonitrile-wat r gradi nt containing 0.1% TFA. Th TFA salt of title compound was obtained as a lyophilized powder.

Anal: ($C_{33}H_{52}N_4O_6S$)					
Calc.	C, 53.09;	H, 6.65;	N, 6.84	1.6 TFA,	0.2 H2O
Found	C, 53.08;	H, 6.66;	N, 6.85		

TLC: R_f 0.10 (80:20:2 CHCl3:MeOH:NH4OH)
HPLC (method A): retention time 8.72 min
FAB MS: m/z 633 (M^+ + H)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (br s, 1H), 7.18 (m, 2H), 7.03 (m, 2H), 2.29 (s, 3H), 1.13 (s, 3H), 0.98-1.01 (overlapping s and d, 6H)

EXAMPLE 57

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(3-(1-ETHOXYCARBONYLMETHYL)-PIPERIDINYLCARBONYL)AMINO)PROPYL-BICYCLO(2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL)PIPERAZINE



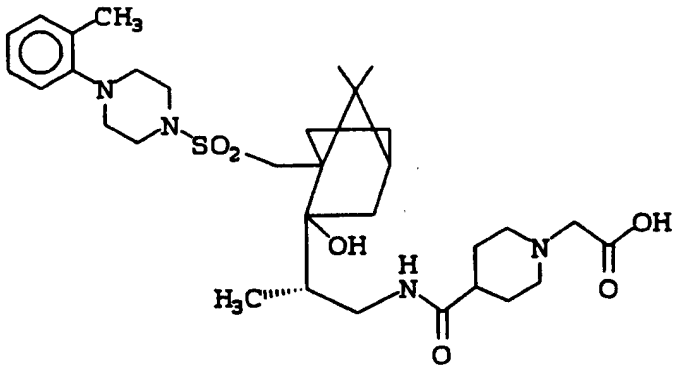
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(3-piperidinylcarbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl)methanesulfonyl)-4-(2-methylphenyl)piperazine (0.20 g; 0.36 mmol) in DMF (5 mL) was added ethyl bromoacetate (0.044 mL; 0.40 mmol) and DIEA (0.070 mL; 0.40 mmol). After 24 h at ambient temperature, the solution was evaporated under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: ($C_{34}H_{54}N_4O_6S$)					
Calc.	C, 52.81;	H, 6.67;	N, 6.57	1.75 TFA,	0.35 H2O
Found	C, 52.80;	H, 6.64;	N, 6.69		

TLC: R_f 0.35 (95:5 CHCl3:MeOH)
HPLC (method A): retention time 9.26 min
FAB MS: m/z 647 (M^+ + H)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (m, 2H), 7.04 (m, 2H), 4.26 (q, J = 7 Hz, 2H), 3.85 (s, 2H), 2.32 (s, 3H), 1.29 (t, J = 7 Hz, 3H), 1.14 (s, 3H), 1.02-1.05 (overlapping s and d, 6H)

EXAMPLE 58

1-((7,7-DIMETHYL-2-EXO-HYDROXY-2-ENDO-2-(1-(4-(1-CARBOXYMETHYL)PIPERIDINYLCARBONYL)-AMINO)PROPYL-BICYCLO (2.2.1)HEPTAN-1-YL)METHANESULFONYL)-4-(2-METHYLPHENYL) PIPERAZINE



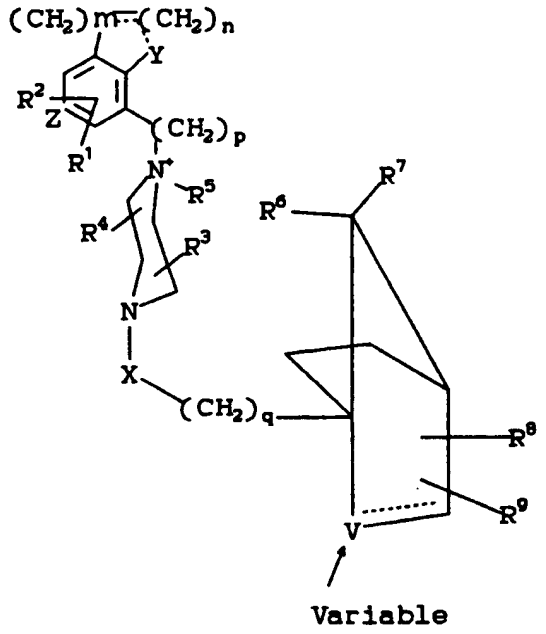
To a stirred solution of 1-((7,7-dimethyl-2-exo-hydroxy-2-endo-2-(1-(3-(1-methoxycarbonyl)-piperidinylcarbonyl)amino)propyl-(2.2.1)bicycloheptan-1-yl) methanesulfonyl)-4-(2-methylphenyl)piperazine (0.15 g; 0.23 mmol) in THF (5 mL) was added 1 M NaOH until a pH 10 solution persisted for 1 h. The solution was evaporated under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of title compound was obtained as a lyophilized powder.

Anal: ($C_{32}H_{50}N_4O_5S$)					
Calc.	C, 53.23;	H, 6.82;	N, 7.18	1.3 TFA,	0.75 H2O
Found	C, 53.20;	H, 6.81;	N, 7.18		

TLC: R_f 0.15 (80:20:2 CHCl3:MeOH;NH4OH)
HPLC (method A): retention time 8.59 min
FAB MS: m/z 619 (M^+ + H)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (br s, 1H), 7.17 (m, 2H), 7.02 (m, 2H), 3.90 (s, 2H), 2.30 (s, 2H), 1.13 (s, 3H), 1.01 (s, 3H), 0.97 (d, J = 6 Hz, 3H)

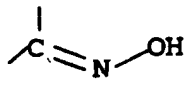
TABLE

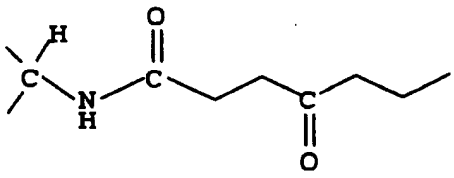
In addition to those compounds specifically exemplified above, additional compounds of the present invention are set forth in tabular form below. These compounds are synthesized by use of the synthetic routes and methods described in the above Schemes and Examples and variations thereof well known to those of ordinary skill in the art, and not requiring undue experimentation. All variables listed in the Tables below are with reference to the following generic structure:

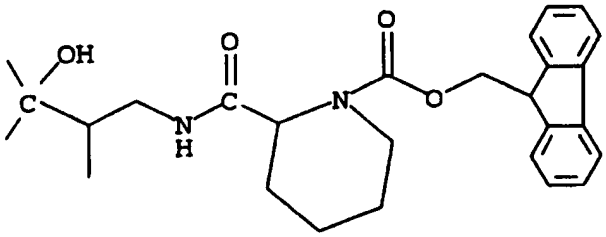


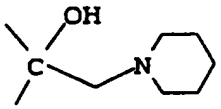
Variable

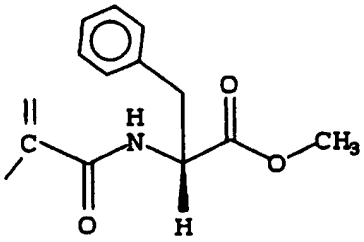
TABLE

V= 









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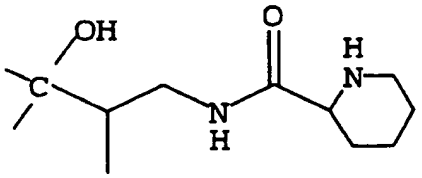

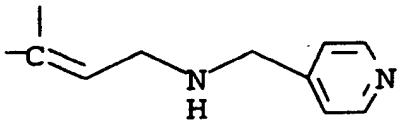

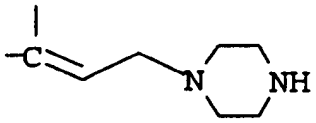

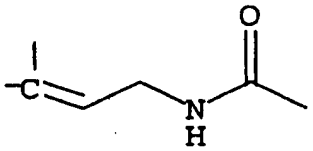

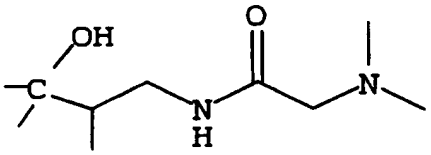

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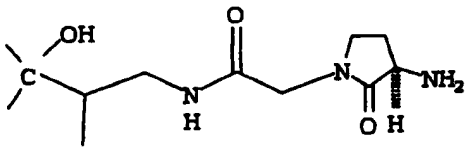

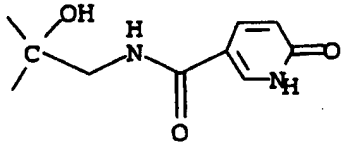

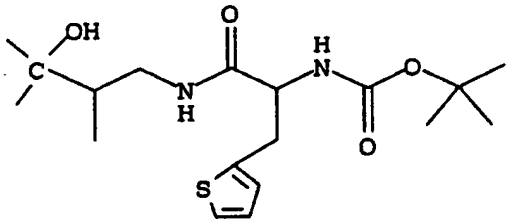

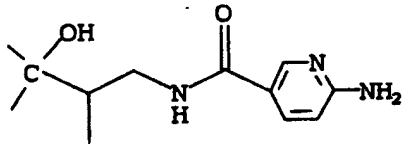

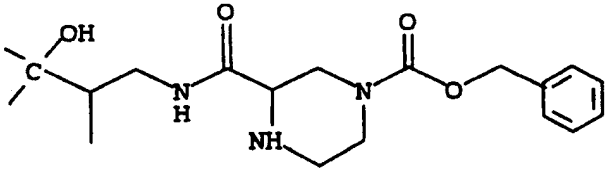

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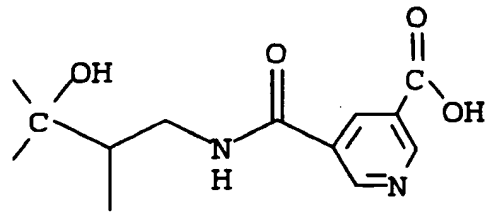

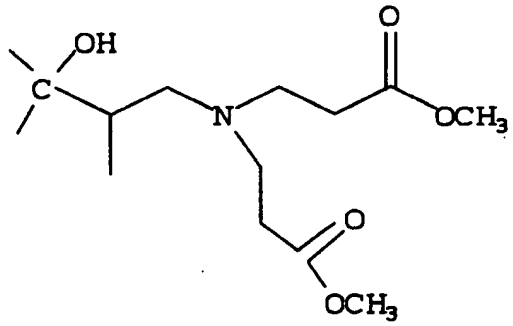

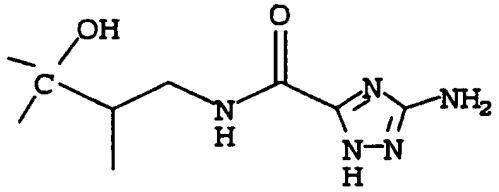

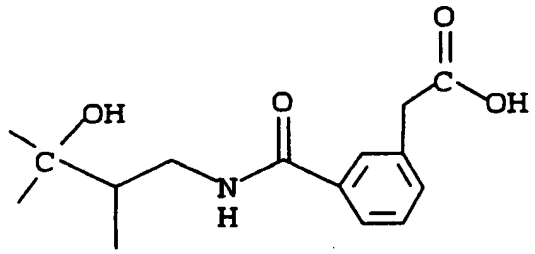

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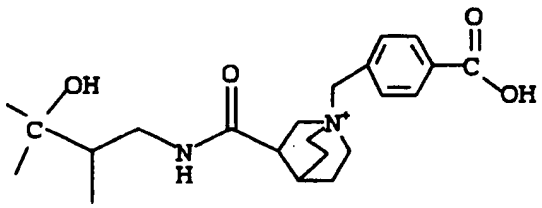

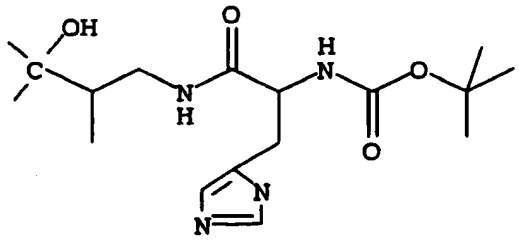

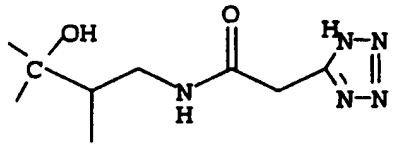

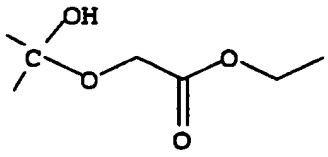

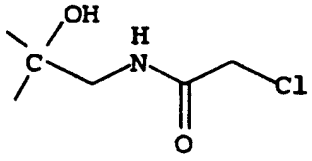

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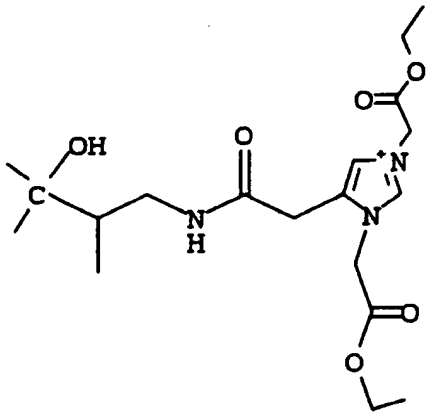

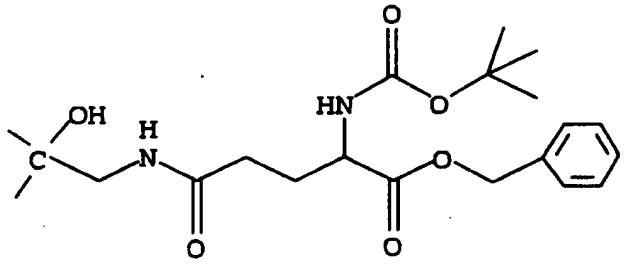

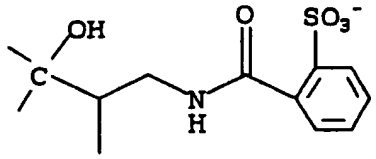

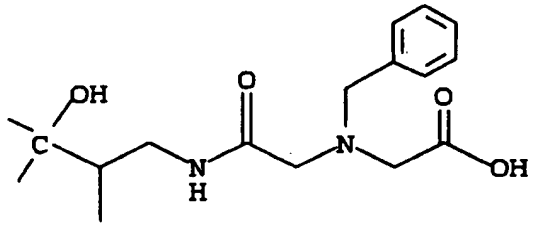

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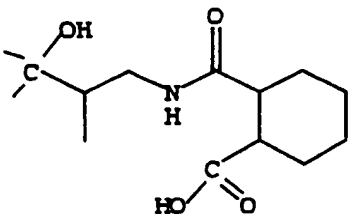

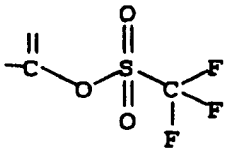

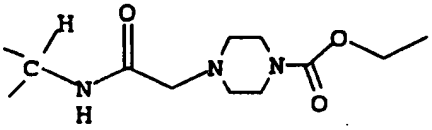

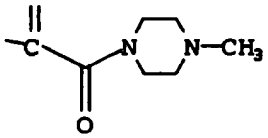

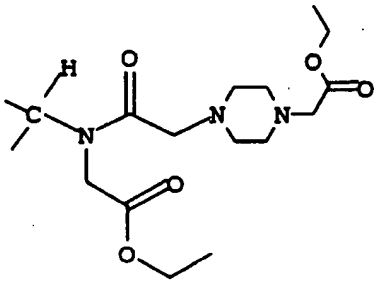

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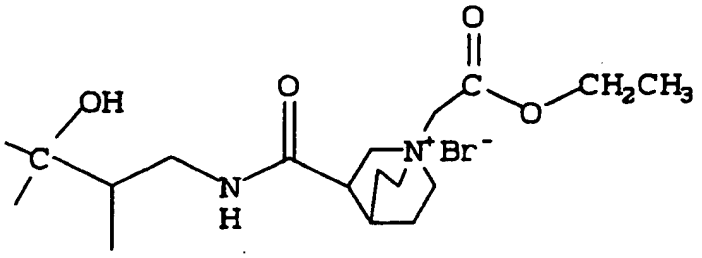

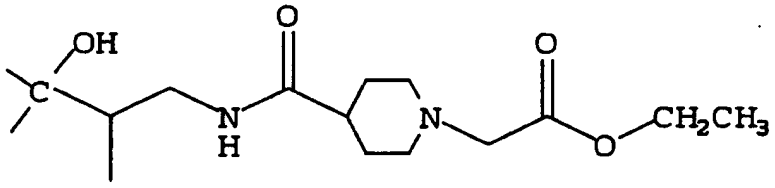

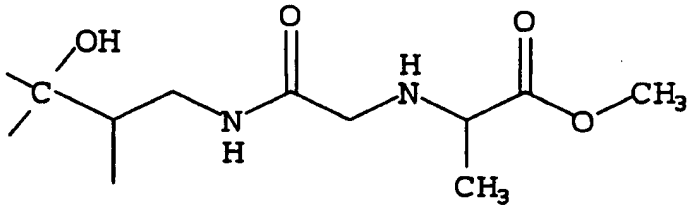

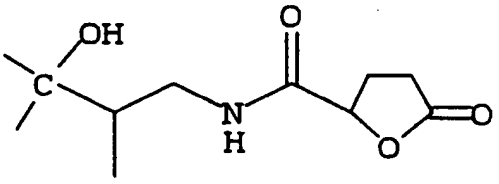

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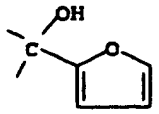

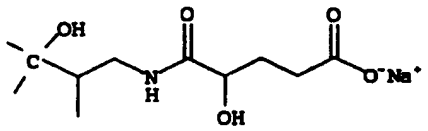

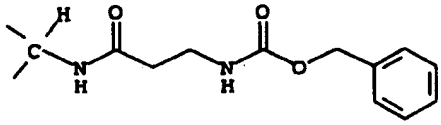

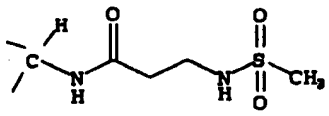

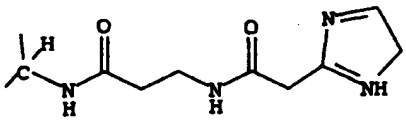

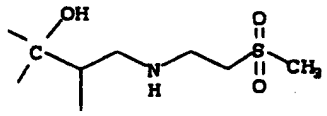

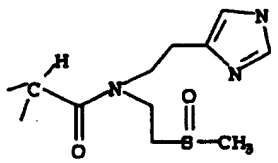

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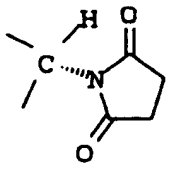
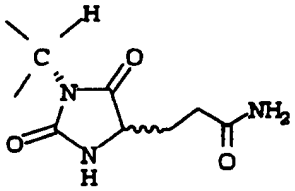
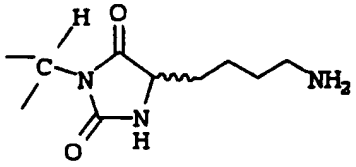
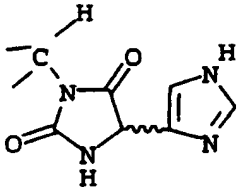
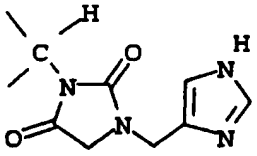
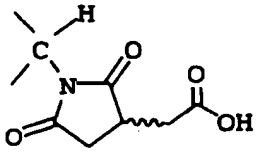




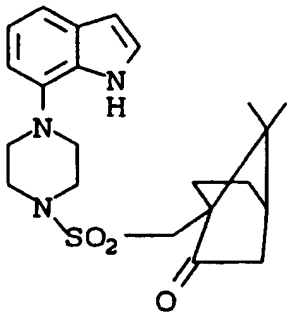


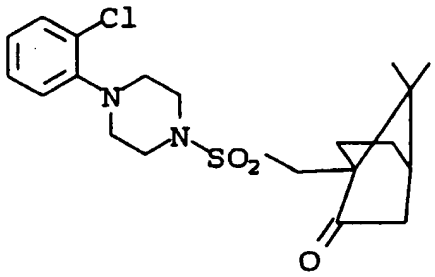


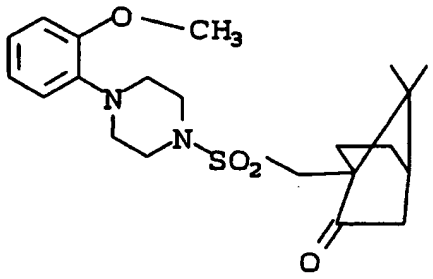


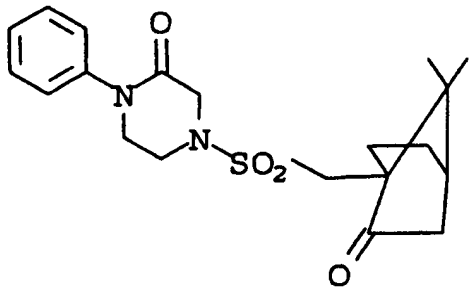


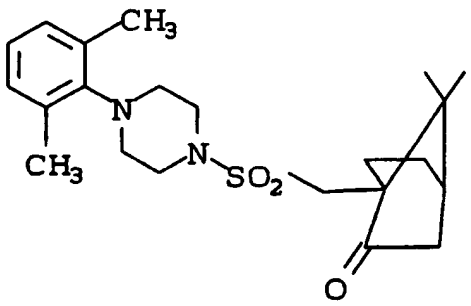
Additional examples of species covered by this invention include the following non-limiting list:

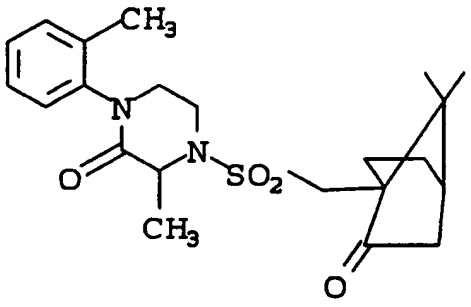


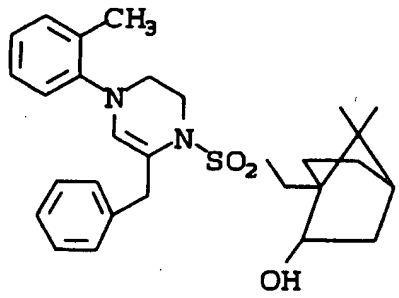


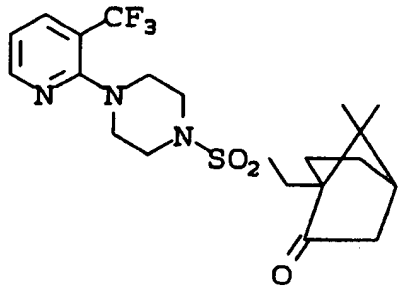


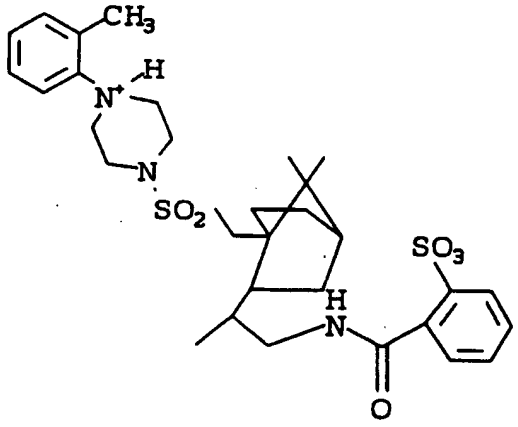












EXAMPLE 33

RADIOGLAND BINDING ASSAYS

The high affinity binding of [^{3}H] Oxytocin (OT)([tyrosyl, 3,5-[^{3}H]OT; 30-60 Ci/mmol; New England Nuclear. Boston, MA) to uterine OT receptors was based on an assay*using a crude membrane preparation of uteri taken from diethylstilbestrol dipropionate (DES)-treated (0.3 mg/kg, ip; 18-24) rats. Competetion studies were conducted at equilibrium (60 minutes; 22 * C) using 1 nM[^{3}H]OT in the following assay buffer: 50 mM Tris-HCl, 5 mM $MgCl_2$, and 0.1% BSA, pH 7.4. Nonsp cific binding (10% of the total binding) was determined using 1μM unlab led OT and the binding reaction was terminat d by filtration through glass fib r filt rs using a cell harvester (model 7019, Skatron, Inc., Sterling, VA). IC_{50} (the concentration of tested compound that inhibits 50% of OT) was reported, unless otherwise noted.

* Fuchs, A-R; Fuchs, F; Soloff, MS. 1985 J. Clin. Endocrinol. Metab. 60:37.

The measurement of [^{3}H]Vasopressin (AVP) ([phenylalanyl-3,4,5-^{3}H]AVP; 80-90 Ci/mmol; New England Nuclear)binding to a crude membrane preparation of male rat liver (AVP-V_1 sites) or kidney medulla (AVP-V_2 sites) was determined according to the method of Butlen, et al.** Competition assays were conducted at equilibrium (30 minutes at 30°C) using 1 nM [^{3}H]AVP (liver) or 2 nM [^{3}H]AVP (kidney) in the following assay buffer: 100 mM Tris-HCl, 5 mM $MgCl_2$, 0.1% BSA, 50 μM phenylmethylsulfonylfluoride, and 50 μg/ml bactracin, pH 8.0. Nonspecific binding (5-10% of the total binding) was determined using 10 μM unlabeled AVP, and the binding reaction was terminated by filtration as described above for the [^{3}H]OT binding assay.

K_i; values were obtained for each compound from three to six separate determinations of the IC_{50} values ($K_i = IC_{50}/1 + c/K_d$)*** using K_d values obtained from saturation binding assay: [^{3}H]OT (uterus), 0.7 nM; [^{3}H]AVP (liver), 0.4 nM; [^{3}H] (kidney), 1.4 nM.

Example	IC_{50}
1	1,000 nM
2	150 nM
3	180 nM
4	34 nM
5	100 nM
6	10 nM
7	8 nM
8	18 nM
9	5 nM
10	48% inhibition at 100 nM
11	54 nM
12	23% inhibition at 100 nM

** Butlen, D; Guillon, G; Rajerison, R.M.; Jard, S; Sawyer, W.H.; Manning, M. 1978 Mol Pharmacol 14:1006.

*** Cheng, Y-C; Prusoff, W.H.; 1973 Biochem Pharmacol 22:3099

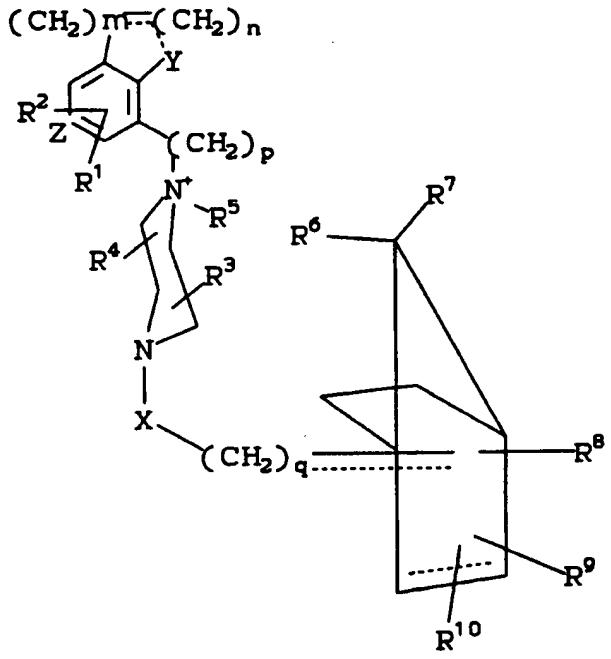
Example	IC_{50}
14	1,100 nM
15	44% inhibition at 1,000 nM
16	64% inhibition at 1,000 nM
17	36% inhibition at 100 nM
18	75% inhibition at 1,000 nM
19	31% inhibition at 1,000 nM
20	72% inhibition at 1,000 nM
21	38% inhibition at 1,000 nM
22	78% inhibition at 1,000 nM
23	120 nM
24	260 nM
25	34% inhibition at 100 nM
26	35 nM
27	37% inhibition at 100 nM
28	35% inhibition at 100 nM
29	78% inhibition at 1,000 nM
30	16% inhibition at 10,000 nM
31	5% inhibition at 10,000 nM
32	37% inhibition at 1,000 nM
33	460 nM
34	-
35	91% inhibition at 100 nM
36	7.7 nM
37	1.2 nM
38	5.4 nM
39	54% inhibition at 1,000 nM
40	35% inhibition at 1,000 nM
41	6.3 nM
42	9.2 nM
43	110 nM

Example	IC_{50}
44	26 nM
	180 nM
45	12 nM
46	20 nM
47	15 nM
48	30 nM
49	25 nM
50	66% inhibition at 100 nM
51	38 nM
52	66% inhibition at 100 nM
53	28 nM
54	14 nM
55	30 nM
56	54 nM
57	66% inhibition at 100 nM
58	56 nM

While the invention has been described and illustrated with reference to certain preferred embodimens thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal being treated for prevention of preterm labor, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

Claims

1. A compound of the formula:



and the pharmaceutically acceptable salts thereof, wherein

X is
(1) carbonyl or
(2) sulfonyl;
Y is
(1) hydrogen,
(2) alkyl or
(3) NH;
Z is
(1) C or
(2) N;
R^1 and R^2 are independently one or more of
(1) hydrogen,
(2) halogen,
(3) alkoxy,
(4) alkylsulfonyl or
(5) unsubstituted or substituted alkyl wherein said substituent is
amino,
alkyl, or
dialkylamino;
R^3 and R^4 are independently one or more of
(1) hydrogen,
(2) alkyl,
(3) substituted alkyl where said substituent is
amino,
alkylsulfonyl,
arylsulfonyl,
alkylamino or
dialkylamino;
(4) phenylalkyl or
(5) oxo;
R^5 is

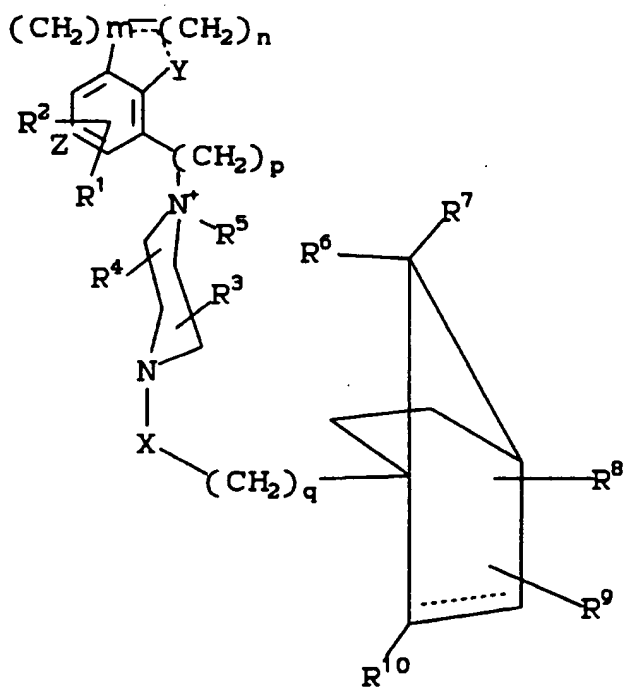
(1) hydrogen or
(2) oxo;

R^6 and R^7 are independently on or more of
(1) hydrogen,
(2) alkyl or
(3) joined to form unsubstituted or substituted cycloalkyl where said substituent is
hydroxy or
hydroxyalkyl;

R^8, R^9 and R^{10} are independently one or more of
(1) hydrogen,
(2) oxime,
(3) hydroxy,
(4) halogen,
(5) cyclic epoxide,
(6) alkylcarbonyloxy,
(7) alkoxycarbonylalkoxy,
(8) trihaloalkylsulfonyloxo,
(9) unsubstituted or substituted 5 or 6-membered heterocyclic rings containing 1,2 or 3 heteroatoms where said heteroatom is N,S or O and said substituents are one or more of
oxo or,
C_{1-6} alkyl, optionally substituted by
alkylthio
alkylsulfinyl
alkylsulfonyl
cyano
carboxy,
hydroxy
amine,
alkylamine
dialkylamine
alkoxy
aminocarbonyl,
tetrazolyl
imidazole and
spiro-piperidinyl where the piperidine
N is unsubstituted or substituted by
C_{1-6} alkyl;
(10) unsubstituted, mono- or di-substituted phenyl where said substituents are independently one or more of
halogen,
carboxy,
alkoxycarbonyl,
carboxyalkyl,
amino,
alkylamino,
dialkylamino,
cyano,
alkylsulfonylamino,
aminoalkyl,
alkylaminoalkyl,
dialkylaminoalkyl; and

m, n, p and q are integers of from 0 to 2.

2. A compound of the formula:



and the pharmaceutically acceptable salts thereof, wherein

X is
- (1) carbonyl or
- (2) sulfonyl;

Y is
- (1) hydrogen,
- (2) alkyl or
- (3) NH;

Z is
- (1) C or
- (2) N;

R^1 and R^2 are independently one or more of
- (1) hydrogen,
- (2) halogen,
- (3) alkoxy,
- (4) alkylsulfonyl or
- (5) unsubstituted or substituted alkyl wherein said substituent is
  - amino,
  - alkylamino or
  - dialkylamino;

R^3 and R^4 are independently one or more of
- (1) hydrogen,
- (2) alkyl,
- (3) substituted alkyl where said substituent is
  - amino,
  - alkylsulfonyl,
  - arylsulfonyl,
  - alkylamino or
  - dialkylamino;
- (4) phenylalkyl or

(5) oxo;

R^5 is

(1) hydrogen or

(2) oxo;

R^6 and R^7 are independently one or more of

(1) hydrogen,

(2) alkyl or

(3) joined to form unsubstituted or substituted cycloalkyl where said is substituent is hydroxy or

hydroxyalkyl;

R^8, R^9 and R^{10} are independently one or more of

(1) hydrogen,

(2) oxime,

(3) hydroxy,

(4) halogen,

(5) oxo,

(6) cyclic epoxide,

(7) alkylcarbonyloxy,

(8) alkoxycarbonylalkoxy,

(9) trihaloalkylsulfonyloxo,

(10) unsubstituted or substituted 5-membered heterocyclic rings containing 1 or 2 heteroatoms where said heteroatom is N or O and said substituents are

oxo or

C_{1-6} alkyl, optionally substituted by

carboxy,

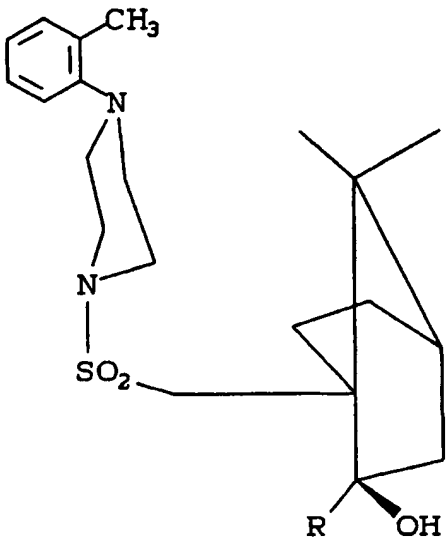
amine,

aminocarbonyl or

imidazole; and

m, n, p and q are integers from 0 to 2.

3. A compound of the formula:



and the pharmaceutically acceptable salts thereof, wherein

R is

(1) hydrogen,

(2) oxime,

(3) hydroxy,
(4) halogen,
(5) cyclic epoxide,
(6) alkylcarbonyloxy,
(7) alkoxycarbonylalkoxy,
(8) trihaloalkylsulfonyloxo,
(9) unsubstituted or substituted 5-membered heterocyclic rings containing 1 or 2 heteroatoms where said heteroatom is N or O and said substituents are independently one or more of
oxo or,
C_{1-6} alkyl, optionally substituted by
carboxy,
amine,
aminocarbonyl or,
imidazole

4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as claimed in claim 1 in an amount sufficient to antagonize the binding of oxytocin to its receptor binding site.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as claimed in claim 1 in an amount sufficient to prevent preterm labor in a mammal.

6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as claimed in claim 1 in an amount sufficient to stop labor prior to cesarian delivery in a mammal.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as claimed in claim 1 in an amount sufficient to treat dysmenorrhea.

8. The use of a compound as claimed in claim 1 for the manufacture of a medicament for antagonizing the binding of oxytocin to its receptor binding site in a mammalian biologic system.

9. The use of a compound as claimed in claim 1 for the manufacture of a medicament for preventing preterm labor in a mammal.

10. The use of a compound as claimed in claim 1 for the manufacture of a medicament for stopping labor prior to cesarian delivery in a mammal.

11. The use of a compound as claimed in claim 1 for the manufacture of a medicament for treating dysmenorrhea in a mammal.

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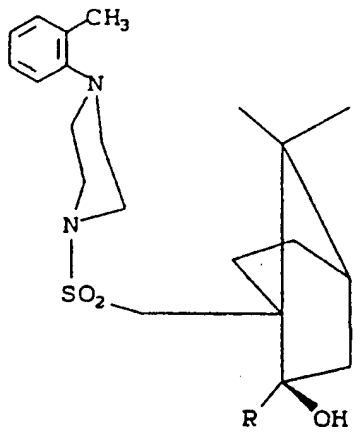
(54) Substituted derivatives of piperazinylcamphorsulfonyl oxytocin antagonists.

(57) Compounds of the formula:



wherein R is oxime, hydroxy, halogen, cyclic epoxide, alkylcarbonyloxy, alkoxycarbonylalkoxy, trihaloalkylsulfonyloxo, or unsubstituted or substituted oxo, where said substituent is unsubstituted or substituted saturated 6-membered heterocyclic rings having 1 or 2 heteroatoms which are N, and said substituent is alkyl.

The compounds of formula I are oxytocin antagonists useful in the treatment of preterm labor, dysmenorrhea and for the stoppage of labor preparatory to cesarean delivery. Also disclosed are pharmaceutical compositions containing these compounds, methods of their use and methods of their preparation.

EP 0 533 242 A3

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 20 2722 • 2

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	US-A-4 147 870 (ANTONIO A. GARCIA) *Document* ---	1-3	C07D295/22 C07D207/26 C07D233/54
A	CHEMICAL ABSTRACTS, vol. 86, no. 5, 31 January 1977, Columbus, Ohio, US; abstract no. 29877c, page 376 ;column R ; * abstract * & ES-A-418 775 (LABORATORIOS LIADE S. A.) ---	1-3	C07D453/02 C07D303/34 C07D211/60 C07D207/16 A61K31/495
A	FR-A-2 081 346 (LABORATORIOS LIADE S.A.) *Document* ---	1-3	
A	FR-A-2 292 477 (LABORATORIOS LIADE S.A.) *Document* ---	1-3	
A	CHEMICAL ABSTRACTS, vol. 78, no. 5, 5 February 1973, Columbus, Ohio, US; abstract no. 29818u, page 510 ;column L ; * abstract * & ES-A-374 515 (LABORATORIOS LIADE) ---	1-3	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
P,A	EP-A-0 486 280 (MERCK) *Document* ---	1-11	C07D
P,A	EP-A-0 450 761 (MERCK) *Document* -----	1-11	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	12 JULY 1993	LUYTEN H.W.

CATEGORY OF CITED DOCUMENTS

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